VOL 8 NO 2 **DANISH MEDICAL BULLETIN** MAY 1961

THE SIGNIFICANCE OF MEGIMIDE IN THE TREATMENT OF BARBITURATE POISONING

By A. MYSCHETZKY

During the years 1954—55, S h a w and his co-workers published a series of articles concerning Megimide, a preparation discovered by them which they considered to have specific antagonistic effects to barbituric acid so that it was capable of counteracting and relieving the narcotic effect of barbituric acid. The chemical composition of Megimide is methyl-beta-ethyl-glutarimide. The compound is manufactured under various names in various countries. In Britain and France it is known as Megimide, in the U.S.A. as Bemegride, in Germany as Eukraton and in Denmark as Glutamisol.

As there was considerable evidence in the articles concerned that a genuine barbiturate antidote was involved, and as a substance with such qualities was naturally of great interest in the treatment of barbiturate poisoning, it was an obvious task for us to evaluate the effect of the substance and its use in the practical treatment of poisoning.

From September 1955 to September 1959, Megimide was employed as a supplement to the routine treatment of poisoning in 250 patients. The great majority of these patients suffered from acute barbiturate poisoning but Megimide was also employed in a number of cases of poisoning with other preparations.

Before the effect of the preparation is discussed in more detail on the basis of observations by the present author and other research workers, a brief account will be given of 222 cases of barbiturate poisoning in which Megimide was employed. The indications for administration of Megimide were clinically severe poisoning either with deep coma and complete absence of reflexes or with respiratory paresis.

From Table 1 the barbiturate preparations employed in these 222 cases, the duration of coma, the maximum concentration of barbituric acid in the blood during hospitalization, the incidence of respiratory paresis and, finally, the number of deaths are apparent.

Out of the 222 cases of poisoning, 120 were comatose for more than 48 hours and of these 40 (*i.e.* one third) for more than 96 hours, and several for 6—7 days. The concentrations of barbituric acid in the blood also reveal that, on the whole, cases of severe poisoning were concerned. Out of the 222 patients, 33, or almost 15 per cent, died, while the average mortality for the patients admitted to *The Centre for Treatment of Poisoning* during the years 1952 to 1955 was about 4 per cent (if cases of slight poisoning which did not warrant admission to *The Centre for Treatment of Poisoning* are included, the mortality for narcotic poisoning in Copenhagen was only 1.5—2 per cent).

The original plan was to attempt to obtain a control material for the Megimide material by administering Megimide only on alternate days. For numerous reasons, such a controlled clinical trial would require a very large number of cases in order to be employable as proof: The lethality is already very low, the individual cases of poisoning are difficult to compare on account of differences in the natures of the narcotics used and the possibility of several poisons being employed together, variations as to the magnitude of the dose taken, the age of the patient and the general condition prior to poisoning, the period of recumbency and the conditions of recumbency prior to admission and possible habituation to the drug, etc.

As, after treatment of the first 200 cases of poisoning with Megimide, it became obvious that considerable disadvantages and risks were associated with the treatment without any obvious advantages being apparent, the treatment was definitively abandoned and thereby also the controlled clinical trial which had been planned.

One of the disadvantages and risks involved in Megimide treatment is spasticity and slight spasms increasing to generalized seizures which must be regarded as an additional strain for these

From the Department of Psychiatry, Bispebjerg Hospital, Copenhagen. (Head: *Carl Clemmesen*).

Table 1.

	Duration of coma in hours				Maximum barbituric acid conc. in blood				Respiratory paresis	Deaths
	No.	< 24	24—48	> 48	< 5 mg %	5—10 mg %	10—20 mg %	> 20 mg %		
Aprobarbital	84	3	19	62	5	52	27	0	22	15
Aprobarbital + Barbital	32	5	14	13	0	4	25	3	5	3
Amytal	25	11	10	4	7	13	4	1	2	0
Phenobarbital	22	5	5	12	1	2	13	6	4	3
Barbital	14	1	4	9	0	0	8	6	4	5
Diverse barbiturates	45	14	11	20	10	19	11	5	8	7
Total	222	39	63	120	23	90	88	21	45	33

patients who are frequently in poor general condition and exhausted. In accordance with the reports by Shaw, one of the objects of Megimide treatment was to bring the patients into a condition of lighter coma ("safe state") with retention of reflex activity (particularly the cough reflex) so that the risk of complications and particularly the risk of hypostasis and atelectasis, should be reduced.

In deeply comatose patients Megimide was, however, often only capable of producing transiently the condition desired. To maintain reflex activity, repeated and considerable doses of Megimide were required and as this obviously placed an extra strain upon the circulation and general condition, it was feared that the oxygen requirement of the brain would also be increased and the general condition thus deteriorate.

Another troublesome complication of Megimide treatment was the strikingly frequent incidence of delirious psychoses after consciousness had been regained. While such psychotic episodes were observed previously in only approximately 3 per cent of the patients (calculated from a material of 2,500 cases of narcotic poisoning) the incidence in the Megimide material was 18 per cent. As described by Kjær-Larsen (4), delirious psychoses apparently of organic origin with confusion, allopsychic disorientation, increased suggestibility and hallucinations which are usually visual, developing 1—4 days after regaining consciousness, were concerned. The psychotic state usually disappeared in the course of 2—6 days.

As it had been demonstrated (Clemmesen (2)) that Megimide was effective in numerous cases of respiratory paresis in barbiturate poisoning, employment of Megimide was continued for some time in cases with this very serious and dangerous complication in barbiturate poisoning for which any effective drug would be welcome. Thus a limited material of respiratory paresis in barbiturate poisoning was obtained which was comparable with previous cases from The Centre for Treatment of Poisoning, cf. Tables 1 and 2.

It will be observed from Table 2 that, employing Megimide, it proved possible to obtain recommencement of respiration in 28 out of 45 cases, *i.e.*, in nearly ⅔ of the cases, while prior to the introduction of Megimide treatment, respiratory pareses could only be relieved in 14 out of 33 cases, *i.e.*, approximately $^2/_5$ of the cases, with the current treatment at that time (amphetamine and Geastimol in small doses). In the Megimide material, respiration recommenced in a number of cases so long after the administration of Megimide (half an hour to several hours after) that the Megimide could scarcely be responsible. It will be observed from Table 2 that, in the control material also, spontaneous remission occurred in a number of cases. Comparisons between the final results in the two groups reveal that respiration recommenced in 42 out of 45 cases in the Megimide group com-

Table 2.
Respiratory paresis.

	Megimide material					Control material				
	Total	Direct effect	Late remission	No change	Deaths	Total	Spontan. remission	Direct effect	No change	Deaths
Aprobarbital	22	12	9	1	5	14	4	8	2	3
Aprobarbital + Barbital	5	5	0	0	2	6	2	1	3	3
Amytal	2	0	2	0	0	3	1	2	0	1
Phenobarbital	4	3	1	0	2	1	0	0	1	1
Barbital	4	3	0	1	4	2	1	1	0	0
Diverse barbiturates	8	5	2	1	3	7	0	2	5	6
Total	45	28	14	3	17	33	8	14	11	14

pared with 22 out of 33 cases in the control group. The mortality in the two groups was approximately $^2/_5$ and $^1/_3$, *viz.*, a very large mortality which was almost equal in the two groups.

Previously, artificial manual respiration admistered with bag and absorber by a nurse or medical student was employed in cases of narcotic poisoning with respiratory paresis. Anaesthetists have demonstrated however, that, even for very experienced anaesthetists, it is impossible to maintain constant ventilation. A mechanical respirator of a simple and reliable type permitting exact adjustment and measurement of respiration was therefore obtained for The Centre.

Since then, neither Megimide nor other stimulants have been missed for these cases. As a rule, respiration recommences spontaneously after a variable period of artificial respiration, particularly if the elimination of the poison can be achieved by means of artificially increasing the diuresis (Lassen (5)).

As mentioned in the introduction, Megimide was put on the market as a specific antidote to barbituric acid. Neither animal experiments (Hahn & Oberdorf (3)) nor the clinical trial of the preparation in The Centre for Treatment of Poisoning, Bispebjerg Hospital, support the antidote theory. Hahn & Oberdorf found, in experiments on cats poisoned with veronal, that the effect of Megimide was comparable to the effects of Cardiazol and picrotoxine, so that Megimide occupies an intermediate position between these drugs although, in its stimulant effect and the effects on the electroencephalogram and blood pressure, it most resembles Cardiazol. Louw & Sonne (8) found that Megimide produced electroencephalographic changes in comatose patients suffering from barbiturate poisoning: reactivation of the more or less extinguished activity occurred; in a great number of the patients examined not only did normal activity reappear but also signs of overstimulation were seen in the form of spikes frequently appearing before any clinical signs of influence by the drug. Both the investigations by Louw & Sonne and by Pedersen (10) revealed that patients who were treated with a Megimide did not regain consciousness with a higher concentration of barbituric acid in the blood nor did the barbituric acid concentration fall more rapidly on treatment as compared with the norms for these conditions established by Lous (6, 7). If a specific antidotic effect had been concerned, either abbreviation of the period of coma or a more rapid fall in the concentration of barbituric acid in the blood in patients treated with Megimide would be anticipated compared with the ordinary clinical course. A third and weighty argument against the presumption of a specific antagonism between Megimide and barbituric acid is to be found in the observation that Megimide has an undoubted effect upon poisoning with substances of quite different chemical compositions. In The Centre for Treatment of Poisoning, Megimide has been observed to have immediate effects on respiratory paresis caused by parathione, thallium and ketobemidone. The seizure-producing effect of the drug mentioned previously, which is merely a clinical manifestation of the cerebral stimulation, expressed by the electroencephalographic changes previously mentioned, must be regarded as evidence for the stimulation theory. The explanation of the strikingly frequent incidence of psychotic phenomena is uncertain. The possibility of a direct psychosis-producing effect of Megimide comparable to those of the known hallucinogenic drugs such as Mescalin and lysergic acid does not appear to be satisfactory, as there is such a long interval between the conclusion of Megimide treatment and the development of the psychosis. Non-specific overstimulation of the brain is perhaps concerned.

To illustrate the effect of Megimide on respiratory paresis in cases of narcotic poisoning which were not due to barbituric acid, the following three case histories are quoted:

1) Female aged 50 years, who had suffered from paranoid schizophrenia for several years, ingested a large dose of rat poison containing thallium sulphate in obedience to her hallucinations. After the elapse of three days she became drowsy and apathetic and ten days after the ingestion of the poison she developed extensive paresis of the extremities of peripheral type, rapidly followed by respiratory paresis which required intubation and artificial respiration. The administration of 0.75 g Megimide intravenously had an immediate but transient effect upon the respiration which became deep and adequate with a frequency of 20 per minute. The infusion, however, had to be discontinued as the patient became very excited with extensive muscular fibrillation. During the state of excitation, the patient extubated herself and died of suffocation as reintubation could not be performed on account of laryngeal spasm.

2) Male aged 36 years drank approximately 100 ml 5 per cent parathione solution with suicidal intent during alcoholic intoxication. On admission, 15 minutes later, he was conscious and in quite good general condition, but after the elapse of 20 minutes, consciousness became clouded and respiratory paresis occurred so that intubation and artificial respiration were necessary. As intensive atropine therapy did not relieve the respiratory paralysis, Megimide was administered 13 hours after admission. Respiration became normal after 0.5 g of this drug and remained so for six hours after which total apnoea developed again. Renewed infusion of 1.5 g Megimide had no effect and the patient died 35 hours after admission.

3) Male aged 21 years was admitted a couple of hours after the ingestion of 750 mg ketobemidone (25 tablets). He was not unconscious but respiration was very slow and inadquate despite repeated doses

of n-allyl-normorphine. Sixteen hours after admission, Megimide was administered intravenously. After the elapse of ten minutes, the respiratory rate had increased from 8 to 16 and in the course of another five minutes to 20 per minute. The infusion of Megimide was discontinued after the administration of 0.45 g on account of repeated vomiting. Respiration remained adequate and the patient recovered.

SUMMARY

A clinical trial of Megimide (Bemegride, methyl-beta-ethyl-glutarimide) in 222 cases of severe barbiturate poisoning showed that in cases of severe poisoning the substance is not able to produce a condition of "safe state" with reestablishment of reflex activity. The drug was found to put an extra strain upon the already exhausted patients and gave an amazingly high percentage of psychotic episodes in the days after awakening. Megimide is looked upon as a central analeptic and not as a specific antidote against barbiturates. It may be of some value in cases of respiratory paresis during narcotic poisoning, but in most cases artificial mechanical ventilation, possibly combined with procedures accelerating the excretion of the poison will be of more value.

Three case histories of successful treatment of respiratory paresis from drugs not containing barbituric acid are given as an indication of the non-specific action of Megimide.

SUMMARIO

A. Myschetsky: LE SIGNIFICANTIA DE MEGIMIDE IN LE TRACTAMENTO DE VENEFICIO DE BARBITURATOS

Shaw e alteres ha considerate Megimide como antidoto specific de acido barbituric. In le Centro de Tractamento de Veneficios in le Bispebjerg Hospital on ha — durante le annos 1955 a 1959 — empleate Megimide como supplemento al tractamento routinari de 250 casos de veneficio, inter quales 222 casos veneficio de barbituratos. Totes representa severissime grados de invenenamento con o coma profunde e complete absentia de reflexos o paralyse respiratori.

Post mentionate 250 casis le administration de Megimide esseva abandonate a causa de obvie avantages e a causa considerabile effectos secundari. Istos es spasticitate e legier spasmos accrescente a convulsiones universal, e item psychoses delirante. Le psychoses commencia 1—4 dies post reganio de conscienta e illos dispare generalmente in le curso de 2—6 dies.

Ni experimentos in animale sexequite per altere investigatores, nu le probas clinic con Megimide i le Centro de Tractemento de Veneficios supporta le conception de on antidoto specific. Le effecto es plus tosto un stimulation cerebral.

Post de introduction a in le Centro de un simple e stabile respirator mechanic on trova superflue e Megimide e altere stimulantes.

References:

1) *Clemmesen, Carl:* Regensburger Jahrbuch f. ärztliche Fortbildung 1960, *VIII: 3:* 202.
2) *Clemmesen, Carl:* Lancet, 1956, *II:* 966.
3) *Hahn, F. & A. Oberdorf:* Naunyn-Schmiedebergs Arch. exp. Pathm. u. Pharmakol., 1957, *231:* 298.
4) *Kjær-Larsen, J.:* Lancet, 1956, *II:* 967.
5) *Lassen, Niels A.:* Lancet, 1960, *II:* 338.
6) *Lous, P.:* Acta pharm. et toxic., 1950, *6:* 227.
7) *Lous, P.:* Acta pharm. et toxic., 1954, *10:* 134, 147, 166, 261.
8) *Louw, A. & L. M. Sonne:* Lancet, 1956, *II:* 961.
9) *Myschetzky, A.:* Paper read in The Danish Psychiatric Soc. Oct. 1959, ref. Nord. Med. 1961, *65:* 239.
10) *Pedersen, Jeppe:* Lancet, 1956, *II:* 965.
11) *Shaw, F. H. et al.:* Nature, 1954, *174:* 402.
12) *Shaw, F. H.:* Med. J. Australia, 1955, *2:* 889.
13) *Shulman, A. & Glenda M. Laycock:* Brit. M. J., 1958, *I:* 871.

IT THE USE OF NEUROMUSCULAR BLOCKING AGENTS CONTRINADICATED IN „POOR RISK" PATIENTS?

By V. DYRBERG and S. H. JOHANSEN

The analysis of anaesthetic deaths in a group of American hospitals by Beecher & Todd (1954) has demonstrated that the use of neuromuscular blocking agents is associated with increased mortality. The underlying factors are undoubtedly complex and varied, but Hunter (1956) has drawn attention to one of these factors in presenting a series of patients, suffering from ileus, in whom the use of myoneural blockers lead to neostigmine-resistant curarization.

The present article is concerned with the choice of anaesthesia based upon the experience gained from eight cases of postoperative respiratory insufficiency following curarization.

CASE MATERIAL

Case No. 1. Male, 57 years old, who had had an extirpation of the rectum for cancer under N_2O-curare-ether anaesthesia. Postoperatively he developed anuria and ileus and a coecostomy was performed on the fourth day under N_2O-gallamine (120 mg) anaesthesia. In spite of a total dose of neostigmine of seven mg the curarization could not be reversed. The respiratory insufficiency lasted until death six days after the last operation and was treated with intermittent positive pressure respiration. He was conscious until two days before death. Hypotension developed during the last days and was treated with infusion of blood and nor-adrenaline. Serum electrolytes on the day of the second operation were normal apart from low chlorides, but hemoconcentration was present as judged from the hemoglobin per cent and the serum proteins. Blood urea was 160 mg.

Case No. 2. Female, 61 years old. One year previously resection of the rectum and sigmoid was done for rectal cancer. Now a laparotomy was performed for renewed intestinal stricture, under spinal analgesia. Since widespread carcinoma was present no further attempts at radical operation were undertaken, but during exploration an intestinal lesion occurred which was sutured. Postoperatively ileus developed, and a second laparotomy was performed on the eleventh day under thiopentone-succinylcholine-d-tubocurarine-N_2O-ether anaesthesia. Muscular relaxation could only be obtained with great difficulty in the face of full doses of curare and addition of ether, and respiratory movements continued throughout the operation. At the end of anaesthesia aspiration from the trachea revealed that she had inhaled considerable amounts of intestinal content. Prolonged respiratory insuffiency with tracheal tug was present, uninfluenced by repeated doses of neostigmine. X-ray examination showed increased density of the lungs and bronchoscopy with aspiration from both bronchi was performed. Respiration never became normal, and although she was treated with intermittent positive pressure respiration she died eight hours after the operation.

Case No. 3. Male, 53 years. Four months earlier an ileo-transversostomy had been performed to relieve a carcinomatous constriction. Because of ileus a colostomy was now performed under cyclopropane-gallamine (80 mg + 40 mg) anaesthesia. To aid closure of the peritoneum 30 mg of succinylcholine was given. For the first three postoperative hours no signs of respiratory activity could be detected, nor could any reaction from stimulation of the trachea or bronchi be evoked. Nikethamide produced no effect. During the following two hours a total dose of 10 mg of neostigmine was administered and the respiration gradually improved to such a degree that it was felt safe to transfer the patient to the ward. Shortly afterwards, however, respiration again became inadequate, necessitating renewed intermittent positive pressure respiration. Hypotension developed and was treated with infusion of nor-adrenaline. The patient died 13 hours after operation. Post mortem examination disclosed widespread carcinoma with perforation of the colon, widespread pneumonia and pulmonary infarction of an inferior lobe. Serum electrolytes on the day of operation were within normal limits, but serum potassium was low (3.4 meq/l).

Case No. 4. Alcoholic male, 63 years old, with a perforated ulcer of the stomach. Laparotomy with closure of the perforation was performed under thiopentone (300 mg)-succinylcholine (75 mg)-d-tubocurarine (30 mg)-N_2O. After the operation repeated doses of neostigmine, totalling 6.75 mg, produced slight and transitory improvement in respiration, but respiratory insufficiency with tracheal tug persisted and cyanosis around the base of the neck developed. Repeated suction through the endotracheal catheter removed great amounts of mucopurulent secretions. Infusion of 1000 ml of blood and one g of potassium chloride in 500 ml of saline produced no conspicuous effects, but very slowly the tidal exchange improved and twelve hours after the operation intermittent positive pressure respiration was discontinued. Suddenly his respiratory condition, however, again deteriorated and severe cyanosis developed in spite of artificial ventilation with pure oxygen. He died thirteen hours after the operation without having regained consciousness. Post mortem examination disclosed diffuse fibrinopurulent peritonitis, large amounts of mucopurulent pulmonary secretions, and total atelectasis of both lower lobes.

Case No. 5. Female, 59 years old, with intestinal obstruction, caused by adhesions to the site of a previous left inguinal herniorrhaphy. Laparotomy was done under thiopentone (150 mg)-succinylcholine (30 mg + 30 mg)-cyclopropane-ether. After the second dose of succinylcholine respiratory insufficiency with tracheal tug persisted throughout the operation and

From the Department of Anaesthesia (Head: *E. Waino Andersen*), Copenhagen County Hospital, Hellerup.

the first eight postoperative hours. During the first three hours intermittent positive pressure respiration was maintained, consciousness returned, and eventually respiration was sufficiently restored to secure adequate oxygenation with an endotracheal tube in place. The tube was removed after one hour, but normal respiration did not return until four hours later. She made an uneventful recovery thereafter. The serum chlorides were 97 meq/l, bicarbonates normal.

Case No. 6. Female, 71 years old, with intestinal obstruction of several days' duration. She had had a right thoracoplasty performed many years previously. As her hemoglobin per cent was 58 she was treated preoperatively with 2000 ml of blood. An intestinal tumour was removed under thiopentone-N_2O with fully paralyzing doses of d-tubocurarine. Respiration did not return till six hours after operation and remained totally inadequate. Circulatory insufficiency was treated with blood and plasma, but she died eight hours after the operation. Post mortem examination revealed a totally atelectatic right lung, atelectasis of the left lower lobe, emphysema of the left upper lobe, and cor pulmonale. Serum chlorides were 81 meq/l, bicarbonate 32 meq/l, blood urea 175 mg per cent on the day of operation. Postoperative ECG indicated cor pulmonale, but did not show signs of hypokalemia.

Case No. 7. Male, 51 years old, with bilateral cavernous tuberculosis of the lungs. After a history of 24 hours of abdominal pain a perforated duodenal ulcer was sutured under thiopentone (400 mg)-d-tubocurarine (37.5 mg)-N_2O anaesthesia. Postoperatively grave respiratory insufficiency with tracheal tug persisted for several hours, unaffected by repeated doses of neostigmine. The respiration gradually returned to normal over six hours. He died six days later. Post mortem examination disclosed a subphrenic abscess and bilateral phthisis. Serum bicarbonate was 16 meq/l and chlorides were 105 meq/l on the day of operation.

Case No. 8. Male, 42 years old, who because of sudden pain in the left side of the chest was admitted to a medical department under the diagnosis of coronary thrombosis. Twelve hours later he was transferred to a surgical department, and, because a perforation of an abdominal viscus was suspected, a laparotomy was immediately performed under thiopentone (300 mg)-succinylcholine (60 mg)-d-tubocurarine (15 mg)-N_2O. The abdominal organs were, however, found normal and the wound was closed. Postoperatively severe respiratory insufficiency with tracheal tug and decreased excursions of the left side of the chest occasioned x-ray examination of the chest which disclosed uniform density on the left side. On thoracotomy a rupture of the oesophagus into the left pleura was found and sutured. Although 3.75 mg of neostigmine had been given the respiration had remained insufficient during the three hours elapsing between the laparotomy and the thoracotomy, and the latter operation was actually carried out under N_2O anaesthesia without additional doses of curare or other agents. Recovery was uneventful. On the morning of the two operations the serum bicarbonate was 38 meq/l. The diagnostic and surgical aspects of this case have been described elsewhere (Andersen & Poulsen 1956).

The case material thus comprises eight patients who all developed gross respiratory insufficiency following the use of myoneural blockers. Five of the patients died without having recovered adequate respiration. All patients were "poor risks" with clinical signs of dehydration and electrolytic imbalance following acute gastro-intestinal pathology of some duration. Four of the patients had widespread intestinal carcinoma, they all died in respiratory insufficiency. Three had perforation of the oesophagus or stomach, one of these survived, one regained full respiratory activity, but died six days later from a subphrenic abscess, and one died in respiratory insufficiency. One case of mechanical intestinal obstruction survived after eight hours of respiratory insufficiency.

Four of the patients had chronically impaired pulmonary function, one aspirated intestinal content, and in one perforation to the pleural cavity had occurred.

DISCUSSION

The above cases strongly indicated that the use of muscle relaxants in these conditions carries grave risks, and consequently a change to inhalational anaesthesia was made, the motivation being that elimination via the lungs always can be relied upon. Over the last five years patients in this category have been anaesthetized with thiopentone-succinylcholine 60 mg—75 mg for intubation and N_2O with ether and/or cyclopropane for maintenance. Additional use of myoneural blockers is avoided. The conditions for surgery under this type of anaesthesia may in some cases have been less ideal than when muscle relaxants with controlled respiration are used. Of greater importance, however, is the fact that, although respiratory insufficiency did occasionally occur following succinylcholine and also at other stages of the anaesthesia, it has always been transitory and has thus never contributed to death.

It is not possible clearly to demonstrate which of the "poor risk" patients in the latter group fall into the category of "curare risks", but it is improbable that such patients have not been encountered during the last five years since the above reported eight cases occurred in the preceding three-year period.

In five out of six cases of prolonged respiratory insufficiency following the use of neuromuscular blockers, reported by Dripps (1953), an element of poor pulmonary function was present. Of four similar cases, reported by Burchell (1957), three presented signs of chronic pulmonary diseases. Among the cases reported in this article six patients out of eight had respiratory impairment at the time of administration of the muscle relaxant.

In the discussion following Hunter's (1956) publication, Rickards (1956) expressed the opinion that the syndrome of neostigmine resistant curarization "is most likely to occur in the

patient with chronic widespread pulmonary disease with a poor vital capacity who is given large amounts of a long-acting myoneural blocking drug".

Other factors, of course, are known to play a part. In our first case the use of gallamine in an anuric patient (Montgomery & Bennett-Jones 1956) undoubtedly was largely to be blamed — but, whatever mechanisms are responsible for producing the syndrome, asphyxia is a prominent feature in the majority of reported cases. Another common characteristic report is electrolytic imbalance, especially potassium depletion (Foster 1956). Several other factors have been brought into the picture (Foldes 1960, The Lancet 1961), but at final evaluation of the cause or causes can hardly be attempted at present, although the indirectly elicited electromyograms employed by Churchill-Davidson (1960) have opened new possibilities for diagnosing persistent neuromuscular block.

The situation facing the anaesthetist is that in a certain proportion of a certain group of "poor risk" patients the production of prolonged neuromuscular blockade is dangerous insofar as complete muscular activity cannot always be restored. This kind of response has been reported after all the commonly used muscle relaxants, whether used singly or in combination. Under these circumstances it seems logical to suggest that an anaesthetic technique which avoids the use of prolonged neuromuscular blockade be preferred in clinical conditions which are associated with dehydration, electrolytic disturbances and poor pulmonary function.

Significantly prolonged apnoea after a single dose of succinylcholine has not been encountered since the adoption of the advocated technique (thiopentone-succinylcholine (60 mg—75 mg)-ether and/or cyclopropane).

SUMMARY

Eight cases of neostigmine-resistant curarization in "poor risk" patients, five of whom died in respiratory insufficiency, are reported. Impairment of pulmonary function was present in six patients at the time of operation.

Inhalation anaesthesia avoiding prolonged curarization has been preferred in similar cases over the last five years and no incidence of prolonged postoperative respiratory insufficiency has been encountered.

Patients developing acute abdominal emergencies of sufficient duration to create fluid and electrolyte imbalance should be considered "curare risks", especially if pulmonary dysfunction is suspected.

SUMMARIO

V. Dyrberg e *S. H. Johansen:* ES CONTRAINDICATE LE USO DE AGENTES NEUROMUSCULO-BLOCANTE IN PATIENTES "DE POVRE RISCO"?

Es referite octo casos de curarisation neostigmine-resistente in patientes "de povre risco", inter qui cinque moriva in insufficientia respiratori. In sex patientes esseva presente al tempore del operation certe deterioration del function pulmonar.

Anesthesia a inhalation sin curarisation prolongate ha essite preferite in casos similar durante le ultime cinque annos, e nulle occurrentia de prolongate insufficientia respiratori postoperative esseva incontrate.

On debe considerar como "povre riscos de curare" omne patientes disveloppante acute e urgente statos abdominal de un duration sufficiente pro disbalanciar le equilibrio fluido-electrolytic. Isto vale specialmente, si il ha suspicion de dysfunction pulmonar.

References:

Andersen, I & T. Poulsen: Ugeskr. Læger 1956, *118:* 690.

Beecher, H. K. & D. P. Todd: Ann. Surg. 1954, *140:* 2.

Burchell, G. B.: Brit. J. Anaesth. 1957, *29:* 127.

Churchill-Davidson, H. C., T. H. Christie & R. P. Wise: Anesthesiology, 1960, *21:* 144.

Dripps, R. D.: Ann. Surg. 1953, *137:* 145.

Foldes, F. F.: Clin. Pharmacol. Therap. 1960, *1:* 345.

Foster, P. A.: Brit. J. Anaesth. 1956, *28:* 488.

Hunter, A. R.: Brit. Med. J., 1956, *2:* 919.

The Lancet (Editorial) 1961, *1:* 34.

Montgomery, J. B. & N. Bennett-Jones: Lancet 1956, 2, 1243.

Rickards, J. F.: Brit. Med. J. 1956, *2:* 1114.

SERUM GLUTAMIC-PYRUVIC-TRANSAMINASE IN INFECTIOUS MONONUCLEOSIS

By THOMAS LAURSEN, VIGGO FABER and PER FROM HANSEN

The involvement of the liver which frequently occurs in infectious mononucleosis was elucidated biochemically and histologically in an extensive report by Bennike (1), who concluded that histological evidence of liver-cell degeneration is rare but that lymphoid infiltration in the liver and swelling of the Kupffer-cells are frequently found. A certain degree of involvement of the liver cells is thus present, and this is borne out by the chemical investigation of the blood which included inter al.—the bromsulphalein test, the thymol turbidity test and serum protein determinations—but not transaminase investigations, which were not part of the clinical routine when the investigation was conducted.

For the demonstration of even a slight degree of liver-cell damage, determination of the concentration of glutamic-pyruvic-transaminase has proved quite helpful, as an increased concentration of this enzyme in the serum usually indicates liver-cell degeneration (7).

Rennie & Wroblewski (6), in a report from 1957, examined 32 patients with infectious mononucleosis and found the serum-glutamic-oxalacetic-transaminase (S-GOT) increased in 25 cases and the serum-glutamic-pyruvic-transaminase (S-GPT) increased in 30 cases. In most cases the increases were moderate, but in almost all of them the increase in S-GPT was greater than the increase in S-GOT; this suggests that S-GPT is a more sensitive indicator of liver-cell damage than is S-GOT, Rennie & Wroblewski also investigated S-GOT and S-GPT in 4 patients with acute tonsillitis and found only an insignificant increase of S-GOT in 1 patient; in other patients with various catarrhal conditions no increase was found.

Other authors (2, 3) who have investigated the serum-transaminase activity in patients with infectious mononucleosis have arrived at similar results. These reports included no examinations of patients with acute tonsillitis.

In the present report, the S-GPT was determined in a group of patients with infectious mononucleosis and in a group of patients with acute tonsillitis; the object was to investigate not only how frequently S-GPT is increased in infectious mononucleosis but also whether the determination of the concentration of S-GPT might be of any help in the differential diagnosis from acute tonsillitis.

The Department of Epidemiology, Blegdamshospitalet, Copenhagen, (Head: *H. C. A. Lassen)*, and The Department of Clinical Chemistry, Rigshospitalet, Copenhagen, (Head: *Poul Astrup)*.

MATERIAL AND METHOD

The material comprises 79 patients admitted to The Department of Epidemiology, Blegdamshospitalet, during the winter of 1957—1958, and 18 patients admitted to The Department of Medicine, Militærhospitalet, Copenhagen in 1959*). Forty patients had definite infectious mononucleosis, 48 definite acute tonsillitis and in nine case it was impossible to decide for certain whether there was infectious mononucleosis or acute tonsillitis.

The diagnoses were established on the clinical, serological and haematological investigations. In 11 cases the diagnosis of infectious mononucleosis was regarded as definite, despite the absence of a positive Paul-Bunnell-reaction (negative reactions in nine cases; reactions not carried out in two cases). The results of the transaminase determination were not received in the clinical department until after the patients had been discharged.

For the estimation of liver function, the thymol turbidity and the cephalin-cholesterol flocculation reactions were employed. In most cases the investigations were made when the patients were admitted, after three days, and then once a week. S-GPT was determined by means of a fluorimetric method (5). The upper limit of normal was taken as 1.8 units.

RESULTS

The results of the investigations in 40 patients with definitive infectious mononucleosis appear from Table 1. Patients whose Paul-Bunnell-reaction was negative or not taken are evaluated separately.

Ninety per cent of the patients with definite mononucleosis were found to have increased S-GPT values; all the patients with negative serum reaction had increased values.

Sixty per cent of the patients had increased thymol turbidity values, and only 38 per cent had increased values for cephalin-cholesterol flocculation reaction.

Out of the 15 patients with normal thymol

*) The authors are indebted to Dr. *F. Neukirch* for permission to use this patient material.

Table 1.

The Distribution of the Figures has been Calculated According to the Maximum Values Found.

	No.	S-GPT			Thymol turbidity			Cephalin-cholesterol flocculation		
		< 1.8	1.8–3.0	> 3.0	Normal	Raised	Not taken	Normal	Raised	Not taken
Infectious mononucleosis. Definite clinical and haematological diagnosis. P. B. positive	29	3	7	19	11	17	1	13	9	7
Infectious mononucleosis. Definite clinical and haematological diagnosis. P. B. negative.	9	0	4	5	3	5	1	6	3	0
Infectious mononucleosis. Definite clinical and haematological diagnosis. P. B. not taken.	2	1	0	1	1	1	0	1	0	1
Total	40	4	11	25	15	23	2	20	12	8

turbidity values 14 had increased S-GPT values, and eight of these had values of over three units. Out of four patients with normal S-GPT one had a normal thymol turbidity level, and three had increased values.

The results of the investigations in the nine patients with no definite diagnosis (infectious mononucleosis) appear from Table 2. It will be observed that the great majority had normal values in the thymol turbidity and cephalin-cholesterol flocculation test, while one third of them had increased S-GPT.

The results of the investigation in 48 patients with acute tonsillitis appear from Table 3.

S-GPT was increased in six out of 48 patients (12 per cent). In practically all the cases there was only a slight increase, only 1 patient having values of over three units (maximum 4.1 units).

The thymol turbidity was also increased in 12 per cent of the cases. Only one patient had a simultaneous increase in both thymol turbidity and S-GPT. The Paul-Bunnell-reaction and the cephalin-cholesterol flocculation test were not carried out in the definite cases of acute tonsillitis.

Table 2.

	No.	S-GPT			Thymol turbidity			Cephalin-cholesterol flocculation		
		< 1.8	1.8–3.0	> 3.0	Normal	Raised	Not taken	Normal	Raised	Not taken
Inf. mononucleosis. Clinical and haematological diagnosis uncertain. P. B. negative.	8	5	2	1	7	1	0	8	0	0
Inf. mononucleosis. Clinical and haematological diagnosis uncertain. P. B. not taken.	1	1	0	0	1	0	0	1	0	0
Total	9	6	2	1	8	1	0	9	0	0

Table 3.

	No.	S-GPT			Thymol turbidity		
		< 1.8	1.8–3.0	> 3.0	Normal	Raised	Not taken
Acute tonsillitis (Blegdamshospitalet)	30	26	3	1	26	4	0
Acute tonsillitis (Militærhospitalet)	18	16	2	0	0	0	18
Acute tonsillitis Total	48	42	5	1	26	4	18

DISCUSSION

The increase of glutamic-pyruvic-transaminase in the serum, which was found in the great majority of patients with infectious mononucleosis, agrees with the investigations mentioned (2, 3 and 6) and with Bennike's (1) view that, in the majority of patients with infectious mononucleosis, there is involvement of the liver-cells although no actual liver-cell degeneration can be demonstrated histologically. Bennike thinks that infectious mononucleosis does not give rise to permanent liver-cell changes. In this material, the increase in S-GPT was purely transient and often lasted for only about a week. In eight patients only there were slight increases which persisted for longer than three weeks. Thus, the increases observed in this material are neither so great nor so prolonged as those observed in epidemic infectious hepatitis.

It is interesting that the patients with a definite diagnosis of infectious mononucleosis based on clinical and haematological findings, but with a negative Paul-Bunnell-reaction, all had increased S-GPT values.

In the group with no definite diagnosis of infectious mononucleosis, 33 per cent were found to have increased S-GPT values; in the group with diagnosis of acute tonsillitis, only 12 per cent were found to have increased values.

An S-GPT determination would alleviate the difficulties involved in the differential diagnosis between infectious mononucleosis and acute tonsillitis, as an increased value would support the diagnosis of infectious mononucleosis. In this material thymol turbidity values were increased in 61 per cent of the cases with a definite diagnosis of infectious mononucleosis. This is in good agreement with the investigations by Iversen & Raaschou, who found increased values in 74 per cent.

These authors recommended the thymol turbidity test as an aid to diagnosis. As the incidence of increased S-GPT is greater than that of increased thymol turbidity, the S-GPT determination would appear to have a greater diagnostic value.

In acute tonsillitis, the incidence of positive values was the same for both tests (12 per cent).

Results of the cephalin-cholesterol flocculation determination show increased values in only 38 per cent of patients with a definite diagnosis. This percentage is much less than those found by other authors; Rennie & Wroblewski (6), for example, found positive results in nearly 100 per cent of the cases. This discrepancy between the two materials may be due to a difference in the reagents or to a different evaluation of the results of this semi-quantitative test.

SUMMARY

In a material of 40 patients with a definite diagnosis of infectious mononucleosis the serum-glutamic-pyruvic-transaminase value was found to be increased in 90 per cent. This increase was transient and disappeared in most cases in less than three weeks.

In nine patients with no definite diagnosis of infectious mononucleosis, S-GPT was increased in 33 per cent; in 48 patients with acute tonsillitis, increase was observed in 12 per cent.

It is concluded that S-GPT determination is a valuable aid in the diagnosis of infectious mononucleosis.

SUMMARIO

Thomas Laursen, Viggo Faber e Per From Hansen:
TRANSAMINASE GLUTAMICO-PYRUVIC SERAL IN MONONUCLEOSIS INFECTIOSE

In un material de 40 patientes con un diagnose definite de mononucleosis infectiose on trovava un augmentation del transaminase glutamico-pyruvic seral in 90 per cento. Iste augmentation esseva transiente e dispareva in le majoritate del casos in minus que tres septimanas.

In nove casos sin un diagnose definite de mononucleosis infectiose TGP seral esseva augmentate in 33 per cento. In 48 patientes con tonsillitis acute un augmentation esseva observate in 12 per cento.

Il es concludite, que determination del nivello de TGP seral es un adjuta valutabile in le diagnose de mononucleosis infectiose.

References:

1) *Bennike, T.:* Studier over leveraffectioner ved mononucleosis infectiosa. Thesis, Copenhagen, 1960.
2) *Brante, G., B. Jønsson, R. Bromø og S. Ericsson:* Svenska Läk. Tidn. 1956, *53:* 2369.
3) *Donato, R. A.:* Am. J. Clin. Path. 1957, *28:* 377.
4) *Iversen, K. & F. Raaschou:* Nord. Med. 1948, *38:* 824.
5) *Laursen, T. & P. F. Hansen:* Scand. J. Clin. Lab. Invest. 1958, *10:* 53.
6) *Rennie, L. E. & F. Wroblewski:* New Engl. J. Med. 1957, 257, 547.
7) *Wroblewski, F. & J. S. LaDue:* Ann. of Int. Med. 1956, *45:* 801.

CONTROLLED ARREST OF ISOLATED PERFUSED RABBIT HEARTS

II. THE SIGNIFICANCE OF TEMPERATURE AND CORONARY CIRCULATION

By CHRISTIAN MOURITZEN and OLE K. ALBRECHTSEN

Previous investigations have revealed that by means of potassium citrate and magnesium sulphate controlled cardiac arrest may be produced on isolated perfused rabbit hearts (Mouritzen & Albrechtsen 1960). These investigations were carried out at 37° C and the coronary circulation was maintained during cardiac arrest. The cardiac action was arrested for 10 minutes and, as a basis for the evaluation of the effect of the ions, both the interval between the commencement of administration of ions until the occurrence of complete cardiac arrest and the ability of the hearts to function again normally after withdrawal of the ionic influence were employed.

The object of the present work was to evaluate the effect of potassium citrate and magnesium sulphate after more prolonged cardiac arrest and to investigate the significance of oxygen deficiency by comparing the results of experiments with maintained and interrupted coronary circulation during the cardiac arrest and, finally, to investigate the protective effect of hypothermia on the possible injurious effects of oxygen deficiency.

MATERIAL AND METHODS

The experiments were carried out on rabbit hearts according to the modification by Baker et al. (1957) of Langendorff's method (1895) as described previously (Mouritzen & Albrechtsen 1960). Following surgical removal of the hearts, the coronary arteries were perfused with pure oxygenized Locke's solution for 10—15 minutes. In the great majority of experiments, regular rhythm and frequency were thereby obtained. The cardiac action was then arrested by perfusion with Locke's solution containing either potassium citrate (18.52 mEq/l) or magnesium sulphate (200 mEq/l), as the previous experiments, mentioned above, showed that these concentrations were best suited to produce controlled cardiac arrest. When cardiac arrest had occurred, the coronary circulation was interrupted in one series of experiments so that the supply of oxygen, nourishment and potassium or magnesium ions was withdrawn while the coronary circulation in the other series of experiments was maintained with subsequent continuous supply of oxygen, nourishment and potassium and magnesium ions during the cardiac arrest. In both series, experiments were carried out at both 37° C and at 29° C. After cardiac arrest for 10, 30, or 60 minutes, the coronary vessels were again perfused with pure, oxygenized Locke's solution. The following criteria were employed in the evaluation of the ionic effect under the experimental conditions mentioned:

1. The interval between perfusion with ions and the occurrence of complete cardiac arrest.
2. The interval until the first cardiac contraction after re-perfusion with Locke's solution.
3. The effect upon the amplitude.
4. The effect upon the frequency.
5. The effect upon the rhythm.

RESULTS

The present experimental series comprised 25 experiments. In addition, the results of the experiments with cardiac arrest for 10 minutes at 37° C and maintained coronary circulation from the abovementioned previous work (Mouritzen & Albrechtsen 1960), which comprises nine experiments with potassium citrate and eight experiments with magnesium sulphate were included for comparison. Each of the experiments in the present series was conducted on a newly removed heart because orientating experiments showed that the results obtained alter somewhat if the hearts have previously been influenced by potassium or magnesium.

The results are apparent from the Table.

1. Interval between perfusion with potassium or magnesium ions and complete cardiac arrest.

Potassium citrate: When the hearts were subjected to the influence of potassium ions at 37° C, complete cardiac arrest occurred after the elapse of 16 to 40 seconds. This interval was more prolonged when the temperature was reduced. Thus, at 29° C, the interval varied between 46 and 70 seconds with the exception of an isolated experiment in which the arrest occurred after 19 seconds.

Magnesium sulphate: The interval until the occurrence of complete cardiac arrest varied between 15 and 34 seconds following subjection to the influence of magnesium ions at 37° C and was thus of the same order as in the potassium experiments at 37° C. Similarly, the interval was prolonged when the temperature was lowered. Thus, it varied between 21 and 105 seconds at 29° C.

Cardiac arrest occurred in different ways at 37° C and at 29° C. While the arrest occurred

From the Institute of Physiology (Head: Prof. *Søren Ørskov*), University of Århus, and the Department of Thoracic Surgery (Head: Prof. *Tyge Søndergaard*), Århus Municipal Hospital, University of Århus.

Table 1.

The Effect of Temperature and Coronary Circulation Upon Cardiac Arrest Produced by Potassium Citrate and Magnesium Sulphate.

		Potassium citrate 18.52 mEq/l				Magnesium sulphate 200 mEq/l			
		With circulation 37° C	No circulation 37° C	With circulation 29° C	No circulation 29° C	With circulation 37° C	No circulation 37° C	With circulation 29° C	No circulation 29° C
10 minutes	Stop	27 sec.	18 sec.	46 sec.	46 sec.	34 sec.	28 sec.	77 sec.	29 sec.
	Start	78 sec.	11 sec.	63 sec.	26 sec.	50 sec.	28 sec.	44 sec.	20 sec.
	Amplitude	100%	100%	100%	100%	92%	100%	100%	100%
	Frequency	Normal	Normal	Normal	Normal	Much reduced	Much reduced	Much reduced	Normal
	Arrhytmia	—	—	—	—	—	—	+	—
30 minutes	Stop	16 sec.	16 sec.	19 sec.	48 sec.	26 sec.	33 sec.	33 sec.	105 sec.
	Start	118 sec.	125 sec.	97 sec.	44 sec.	194 sec.	286 sec.	35 sec.	75 sec.
	Amplitude	100%	95%	100%	100%	33%	50%	100%	100%
	Frequency	Normal	Much reduced	Normal	Normal	Much reduced	Much reduced	Much reduced	Much reduced
	Arrhytmia	—	—	—	—	—	—	—	—
60 minutes	Stop	40 sec. 16 sec.	26 sec. 25 sec.	66 sec.	66 sec. 70 sec.	31 sec.	15 sec.	21 sec.	44 sec.
	Start	158 sec. 105 sec.	— —	128 sec.	110 sec. 40 sec.	—	—	352 sec.	167 sec.
	Amplitude	90% 100%	0% 0%	67%	50% 64%	0%	0%	50%	60%
	Frequency	Normal Normal	0 0	Normal	Normal Much reduced	0	0	Much reduced	Much reduced
	Arrhytmia	— —	0 0	—	— —	0	0	—	—

quite suddenly at 37° C without any significant alteration of the amplitude, the reduction of the temperature caused considerable reduction of the amplitude, following which the action of the heart continued with the reduced amplitude for some time until it finally ceased completely.

2. Interval between re-perfusion with Locke's solution and the first contraction of the heart.

The longer the duration of the cardiac arrest, the later did the cardiac action recommence following re-perfusion with pure, oxygenated Locke's solution.

In the experiments in which the coronary circulation was interrupted during the period of cardiac arrest, the cardiac action recommenced more rapidly following cardiac arrest for 10 minutes than in the cases in which the coronary circulation had been maintained during the arrest. On the other hand, cardiac action did not recommence after cardiac arrest for 60 minutes if the coronary circulation had been interrupted. This observation, however, only holds true at 37° C while at 29° C there was a tendency for the heart action to recommence more rapidly if the coronary circulation had been interrupted during cardiac arrest for 60 minutes.

Where the brief arrest for 10 minutes was concerned, the interval until the recommencement was not influenced by alterations in the temperature. Following a period of cardiac arrest for 30 minutes, a definite difference was observed, the interval until recommencement being considerably briefer in experiments at 29° C than at 37° C. The difference was even more pronounced following cardiac arrest for 60 minutes. Employing potassium citrate, cardiac action did not recommence after experiments with interrupted coronary circulation at 37° C, while in corresponding experiments at 29° C, heart action recommenced after 110 and 40 seconds, respectively. Employing magnesium sulphate, the difference was even more pronounced as none of the hearts in experiments at 37° C and periods of cardiac arrest of 60 minutes recommenced while, in the corresponding experiments at 29° C, cardiac action recommenced after intervals of 352 and 167 seconds, respectively.

The intervals until recommencement following cardiac arrest for 10 and 30 minutes with mag-

nesium sulphate were of the same order as in experiments with potassium citrate. After cardiac arrest for 60 minutes, on the other hand, there was a definite difference: in the experiments with magnesium sulphate it proved impossible to get heart action to recommence at 37° C while this was only the case where potassium citrate was concerned at 37° C and with interruption of the coronary circulation. In the experiments where the cardiac action recommenced, the interval until recommencement took place was considerably longer in the experiments with magnesium sulphate.

3. Effect upon the amplitude.

The amplitude is expressed as a percentage of the original amplitude prior to subjection to the ionic influence.

Following cardiac arrest for 10 and 30 minutes with potassium citrate, the amplitude on recommencement was practically uninfluenced by the arrest.

After cardiac arrest for 60 minutes with potassium citrate, the amplitude was only unchanged in experiments at 37° C and with maintained coronary circulation. At 37° C and with interrupted coronary circulation during the arrest, the heart action did not recommence and, at 29° C, the amplitude in all of the experiments was reduced to approximately half of the original amplitude.

Alteration of the amplitude was more pronounced in the experiments with magnesium sulphate. Here, normal amplitude was only found in all of the experiments after cardiac arrest for 10 minutes. Following cardiac arrest for 30 minutes, the amplitude was only normal if the temperature had been reduced to 29° C and was considerable reduced in experiments at 37° C.

Following cardiac arrest for 60 minutes, heart action did not recommence at 37° C while at 29° C it only recommenced with considerable reduction of the amplitude.

4. Effect upon the frequency.

The alteration of the frequency following cardiac arrest was evaluated three minutes after the first contraction by estimation of the degree of marking of the paper on the drum on which the cardiac action was recorded.

Following cardiac arrest produced by potassium citrate, the frequency was uninfluenced in the experiments where the coronary circulation was maintained during cardiac arrest. If the coronary circulation was interrupted during the cardiac arrest, the frequency was considerably reduced after cardiac arrest for 30 minutes at 30° C while, as mentioned previously, cardiac action did not recommence again after cardiac arrest for 60 minutes. If the temperature were lowered to 29° C under these conditions, the frequency was not influenced until after cardiac arrest for 60 minutes.

The frequency was considerably reduced in practically all experiments with magnesium sulphate.

5. Effect upon cardiac rhythm.

In the present series of experiments, arrhythmia was only observed after recommencement in an isolated experiment (following perfusion with magnesium sulphate, cardiac arrest with maintained coronary circulation for 10 minutes at 29° C).

DISCUSSION

Among the series of substances which are known to produce controlled cardiac arrest on isolated perfused hearts, potassium citrate and magnesium sulphate have hitherto proved to be the most suitable (Baker et al. 1957, Melrose et al. 1955, Merritt et al. 1958, Mouritzen & Albrechtsen 1960). The present investigation is concerned with the effects of these ions under various experimental conditions.

The interval between the commencement of perfusion with potassium citrate or magnesium sulphate at 37° C and the occurrence of complete cardiac arrest was of the same order in these experiments as that previously observed. On the other hand, a prolongation of this interval was observed when the temperature was reduced to 29° C.

The interval from the commencement of reperfusion until the first contraction became longer, the longer the period of cardiac arrest. Simultaneously, certain effects were observed upon the amplitude and the frequency. This holds true, whether the coronary circulation was maintained or interrupted during the period of cardiac arrest and is probably expression of the injurious effect of the ions in question, in the former case, and, in the latter case, expression of deficiency of oxygen and nourishment during the experiment. These conditions were most pronounced in the experiments with magnesium sulphate and, thus, the previous observation that the magnesium ion has a more injurious effect on the isolated heart than the potassium ion is confirmed. Even after cardiac arrest for 10 minutes, considerable reduction of the frequency and commencing effect upon the amplitude were observed after perfusion with magnesium sulphate while similar changes were not found in the experiments with potassium citrate. Similarly, the hearts did not recommence following continuous perfusion with magnesium sulphate for 60 minutes at 37° C, while perfusion with potassium citrate under the same experimental conditions had only a slight effect upon the hearts.

Reduction of the temperature from 37° C to 29° C appeared to protect from the injurious effects of the perfusing ions to a certain extent.

This was most apparent in the magnesium experiments in which the injurious effect was already greatest. While at 37° C a considerable effect both upon the amplitude and the frequency was found following cardiac arrest for 30 minutes of continuous perfusion with magnesium sulphate and complete cessation of cardiac action after cardiac arrest for 60 minutes, reduction of the temperature permitted considerably better action after cardiac arrest for 30 minutes and, after 60 minutes, the cardiac action was able to recommence although weakened.

The question of how long the supply of oxygen can be interrupted after cardiac arrest without damage to the heart was investigated previously. Thus, Baker et al. (1957) found that, after having produced cardiac arrest with potassium citrate at 37° C on isolated hearts, the coronary circulation may be interrupted for a maximum of 30—45 minutes without significant effect upon the amplitude. Similarly, it was recorded that reduction of the temperature in the experiments with interrupted coronary circulation protected the hearts from the injurious effect of oxygen deficiency so that after cardiac arrest for 30 minutes an amplitude of 100 per cent of the original was obtained after re-perfusion. Finally, Melrose et al. (1955) report that the oxygen consumption of the non-working heart is so negligible that the coronary circulation may be interrupted for over 15 minutes at 37° C without damage to the heart. These results are confirmed in the present experiments.

Thus, it was observed that while cardiac action cannot be re-established at 37° C after cardiac arrest for 60 minutes, if the coronary circulation, and therefore the supply of oxygen, were discontinued during the period of cardiac arrest, heart action could be re-established again under these experimental conditions if the temperature was reduced to 29° C. This holds true both for the experiments with potassium and magnesium.

Baker et al. (1957) emphasized that with maintained coronary circulation with continuous administration of potassium citrate during the entire experimental period, poorer amplitudes were observed than if the coronary circulation had been interrupted. In contrast to this, in the present experiments with continuous administration of potassium citrate in the experiments with cardiac arrest at 37° C, unchanged amplitude and frequency following re-perfusion with pure Locke's solution were obtained, while after cardiac arrest for 60 minutes, the experimental conditions being otherwise the same, normal frequency and an amplitude of 90—100 per cent of the original were similarly observed. If the coronary circulation was interrupted during the period of cardiac arrest, however, both the amplitude and the frequency were influenced already after 30 minutes while cardiac action could not be re-established after cardiac arrest for 60 minutes. The withdrawal of administration of oxygen and nourishment in experiments with interrupted coronary circulation thus appears to damage the heart to a greater extent than the continuous administration of potassium during the experiment.

The present results thus show that potassium citrate is preferable to magnesium sulphate for the production of controlled cardiac arrest in isolated rabbit hearts. If the cardiac arrest produced by potassium citrate is to be of brief duration (10 minutes), uniform results are achieved at 37° C and 29° C. On the other hand, the first contraction after the cardiac arrest occurs more rapidly if the coronary circulation is discontinued during the period of cardiac arrest. If the cardiac arrest is to be for a longer period (30 minutes) the administration of oxygen and nourishment should not be discontinued during the period of cardiac arrest, if the temperature is maintained at 37° C while this condition is of less significance if the temperature is reduced to 29° C. Finally, if the period of cardiac arrest is to be for longer than 60 minutes, the best results are observed if the coronary circulation is maintained during the period of cardiac arrest at 37° C and reduction of the temperature to 29° C does not improve the results thus obtained.

SUMMARY

Comparative experiments concerning the ability of potassium citrate and magnesium sulphate to produce cardiac arrest at 37° C and 29° C with maintained and interrupted coronary circulation for 10, 30 and 60 minutes, respectively, showed the following results:

1. The interval from the commencement of the administration of ions until the occurrence of cardiac arrest seems to increase if the temperature is lowered.
2. The interval from the withdrawal of ion administration until the first cardiac contraction after total cardiac arrest is prolonged the longer the period of cardiac arrest.
3. The magnesium ion has a more injurious effect on the isolated heart than the potassium ion.
4. Arrhythmia is a rare phenomenon after cardiac arrest caused by potassium citrate and magnesium sulphate.
5. Reduction of the temperature to 29° C protects the isolated heart to a certain extent from the injurious effects of the ions.
6. Reduction of the temperature to 29° C protects the heart from the injurious effects of oxygen deficiency.
7. The period in which the heart can dispense with the coronary circulation at body temperature without significant alteration of the amplitude and frequency is scarcely more than 30 minutes.
8. Withdrawal of oxygen administration for 60

minutes during total cardiac arrest appears to damage the heart more than continued administration of potassium ions for 60 minutes.

This work was conducted with support from The King Christian X Fund.

The authors express their gratitude to Dr. J. Chr. Skou of the Department of Physiology, University of Århus, for his interest and assistance in the conduct of this research.

References:

1) *Baker, J. B. E., H. H. Bentall, B. Dreyer & D. G. Melrose:* Lancet 1957, *2:* 555.
2) *Langendorff, O.:* Arch. Physiol. 1895, *61:* 291.
3) *Melrose, D. G., B. Dreyer, H. H. Bentall & J. B. E. Baker:* Lancet 1955, *2:* 21.
4) *Merritt, D. M. H., W. C. Sealy, W. C. Young, Jr. & J. S. Harris:* Arch. Surg. 1958, *76:* 365.
5) *Mouritzen, C. & O. K. Albrechtsen:* Dan. Med. Bull. 1960, *7:* 134.

SUMMARIO

Christian Mouritzen & Ole K. Albrechtsen: ARRESTO CONTROLATE DE ISOLATE E PERFUNDITE CORDES DE CONILIOS. — *II. Significantia de temperatur e circulation coronari.*

Esseva executate experimentos comparative concernente le potentia de citrato de kalium e sulfato de magnesium de producer arresto cardiac a 37 C e 29 C con circulation coronari mantenite e interrupte durante 10, 30 e 60 minutas respectivemente. Esseva trovate le resultatos sequente:

1. Pare augmentar le intervallo inter initio de administration de ions e comenciamento de arresto cardiac si le temperatura es bassate.
2. Es prolongate le intervallo inter arrestation de administration de ions e prime contraction cardiac post arresto cardiac total secundo plus longe duration del arresto.
3. Le ion de magnesium possede un effecto plus injuriose que illo del ion de kalium super le corde isolate.
4. Arrythmia es un rar phenomeno post arresto cardiac causate per citrato de kalium e sulfato de magnesium.
5. Reduction del temperatura a 29 C protege a certe extension le corde isolate contra le effectos injuriose del ions.
6. Reduction del temperatura a 29 C protege le corde contra le effectos injuriose de deficientia de oxygeno.
7. Le periodo in le qual le corde pote, a temperatura de corpore, esser in carentia de circulation coronari sin alteration significante del amplitude e frequentia superpassa a pena 30 minutas.
8. Arrestation del administration de oxygeno per 60 minutas durante total arresto cardiac pare esser plus damnose al corde que administration continue de ions de kalium per 60 minutas.

PIGMENT CHANGES IN THE LUMBAR FLUID AS A DIAGNOSTIC AID IN INTRACRANIAL HAEMORRHAGIC LESIONS

By V. KRONHOLM and J. LINTRUP

Counting of red cells in the cerebrospinal fluid has long been the most important aid in diagnosing haemorrhagic lesions in the central nervous system. Less attention has been paid to the CSF content of free pigments after centrifuging off the red cells. After the introduction of the spectrophotometer, however, objective measurements may be performed, even of minute pigment concentrations (Heilmeyer 1933).

It was known already that xanthochromia is caused by varying quantities of oxyhaemoglobin and bilirubin and that furthermore the haematoma fluid in subdural and intracerebral haematomas has a high concentration of methaemoglobin (Barrows, Hunter & Banker 1955).

From the Department of Neurology (Head: *T. Dalsgaard-Nielsen*) and Central Laboratory (Head: *A. Levin Nielsen*), Frederiksberg Hospital, Copenhagen.

Extension of the studies to the Soret band of the haemoglobins in the near-ultraviolet part of the spectrum later showed that methaemoglobin also occurs commonly in the xanthochromic spinal fluid, where it may be the prevailing component in the presence of intracranial haematoma (Kronholm & Lintrup 1960).

To elucidate the clinical value of such pigment studies, we shall report two characteristic cases of intracranial haemorrhagic lesions investigated by the above method.

CASE HISTORIES

Case 1. A woman aged 64. Eight years prior to admission she had had a "stroke" involving right-sided hemiparesis, but she recovered completely, so that she was able to look after herself and her shop. Two hours before admission she suddenly had another stroke, and when admitted she was deeply uncon-

Table 1.

Case 1. Findings in 6 Consecutive Lumbar Punctures. E_{415} Indicates Optical Density at 415 nm. The Calculated Concentrations of Total Haemoglobin (= Oxyhaemoglobin + Methaemoglobin) and Bilirubin are Stated in μmol/l and Methaemoglobin in per cent of Total Haemoglobin. Brackets Denote that the Value Concerned is Insignificant, Being Relatively so low as to be Estimated as Lower than the Uncertainty of the Calculation.

Time after the stroke	3 hours	3 days	7 days	10 days	30 days	56 days
Red cells per cu mm ...	9,500	3,300	60	1,100	9	1
E_{415}	0,126	0,580	0,325	3,500	0,096	0,020
Total haemoglobin, μM	0.8	(0.9)	1.5	30	0.6	0.0
Bilirubin, μM	0.5	13	3.6	(4.2)	0.6	0.0
Methaemoglobin, per cent	(20)	(9)	45	54	70	—
Protein, mg/100 ml	174	260	56	150	44	33

scious, showing total left-sided hemiplegia. At the end of four weeks there was some improvement in consciousness, but the patient never became really awake. The hemiplegia remained total, and death from bronchopneumonia occurred four months after admission.

Arteriography of the right internal carotid artery showed no displacement of the vessels, no particularly marked arteriosclerosis, and no signs of thrombosis.

Electroencepalography was severely abnormal, showing right-sided preponderance without a distinct focus.

Lumbar puncture was done six times, and the results are shown in Table 1. The pigment study comprised measurements of the spectral absorption curve between 390 nm and 500 nm (Figs. 1—3) on the basis of which the pigment concentrations were calculated (Kronholm & Lintrup 1960).

Post-mortem examination of the brain: On the right side, a haemorrhage, the size and shape of a date, in the caudate nucleus and internal capsule. In a limited area, this bleeding had penetrated to the ventricular system, but the aperture had again closed, so that no blood was present in the ventricle. In the left internal capsule an old, fissure-shaped bleeding. No atherosclerosis or thrombosis in the vessels.

Case 2. A widow, aged 88, who had always been in good health. She was admitted to a medical department because of dizziness. A few times she had had a fall in the street, but without loss of consciousness. Mentally she was alert. No headache. Blood pressure and haemoglobin level normal. No signs of heart disease. During her stay in the medical department she developed transitory paresis of the left-sided extremities.

Because of a suspicion of right-sided carotid thrombosis, the patient was transferred for assessment to the Neurological Department. Fig. 4 gives the results of the investigation of the spinal fluid. Electroencephalography revealed a degenerative focus on the

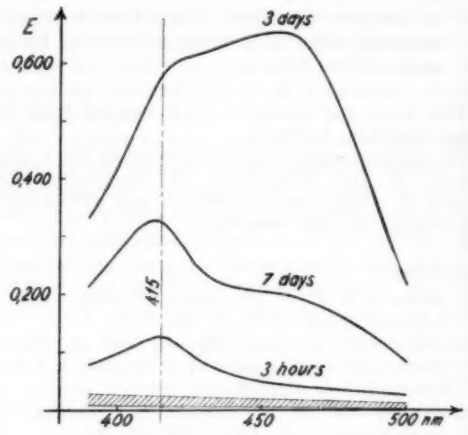


Fig. 1.

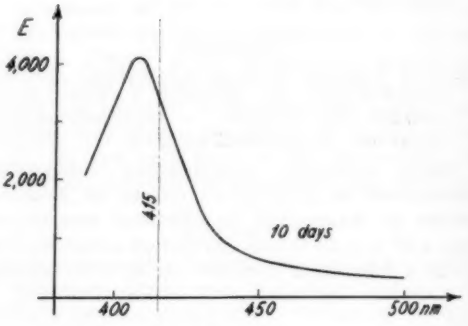
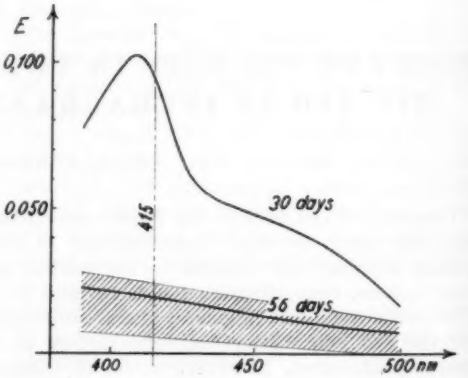


Fig. 2.



Figs. 1—3.

(Case 1). The Changing Spectral Absorption Curves During the Course of the Disease. Normal Range Hatched. (Note the Highly Varying Scale Along the Ordinate).

right side and carotid arteriography a two cm deep, avascular zone over the right hemisphere.

The patient was now transferred to a department of neurosurgery, where a right-sided subdural haematoma with fluid contents and well-marked membranes was evacuated. Uneventful postoperative course.

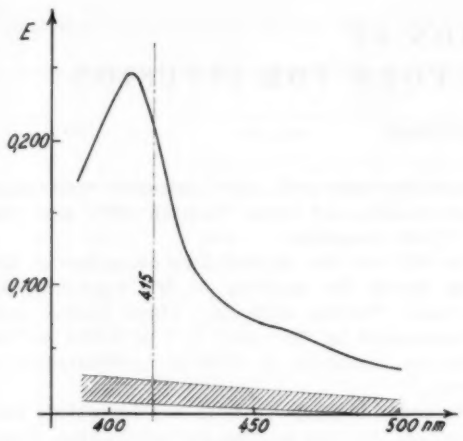


Fig. 4.

(Case 2). Absorption Curve in Subdural Haematoma. Red cell Count 123 per cu mm. Protein: 65 mg per 100 ml. Calculated Pigment Concentrations: Bilirubin 0.6 µmol/l. Total Haemoglobin 1.6 µmol/l. Methaemoglobin 75 % of Total Haemoglobin.

COMMENTS

Case 1. The curve, traced three hours after the stroke, showed mainly oxyhaemglobin*). This is characteristic of fresh subarachnoid aneurysmal bleeding or accidental blood admixture because of traumatic lumbar puncture. It may be seen, however, also during the first hours after cerebral haemorrhage. The next tracing, done three days later, however, leaves no room for doubt, showing an almost pure bilirubin curve. This is characteristic of cerebral haemorrhage or contusion at this stage and is not observed so soon after subarachnoid aneurysmal bleeding and never in cases of accidental blood admixture.

Seven days after the episode, there was again haemoglobin in the spinal fluid, almost equally distributed between oxy- and methaemoglobin. This is unusual, since cerebral haemorrhages generally show pure bilirubin curves of decreasing height at this juncture. New haemorrhage would explain this finding, but it does not appear likely, since the number of red cells was negligible and the patient's condition remained unchanged. The most satisfactory explanation is the formation of a haematoma in the vicinity of the subarachnoid space from which haemoglobin derivatives have found their way into the CSF.

On the 10th day the optical density of the CSF had increased enormously, the tracing being distinctly characterized by methaemoglobin with a shift of the maximum towards 406 nm. Such extreme increase in the concentration of haemoglobin derivatives combined with a low content of red cells indicates the existence of a perforation aperture between a haematoma with haemolysed blood and the subarachnoid space.

The next tracing, 30 days after the episode, showed greatly decreasing pigment concentrations, but still characterized by haemoglobin derivatives. On the 56th day the lumbar fluid had returned to normal. The assumption is, therefore, that at this stage the haematoma had become completely encapsulated from the subarachnoid space.

These assumptions regarding the course of events, based upon contemplations regarding the pigment pattern in the CSF, seem to have been proved by post-mortem examination of the brain four months after the stroke.

Case 2. The lumbar fluid was slightly xanthochromic, methaemoglobin being the most outstanding pigment. The red cell count was fairly low. Such a pattern is not encountered in cerebral haemorrhage or thrombosis, indicating rather a haematoma, intracerebral or subdural. The site of the lesion was disclosed by electroencephalography and arteriography.

SUMMARY

A description is given of (1) a case of cerebral haemorrhage in which a highly varying pigment pattern in the lumbar fluid permitted certain deductions regarding the course of the disease process in the brain and (2) a case of chronic subdural haematoma in which the pigments of the CSF afforded the diagnosis of haematoma.

SUMMARIO

V. Kronholm & J. Lintrup: ALTERATIONES PIGMENTARI DEL LIQUIDO SPINAL COMO GUIDA DIAGNOSTIC IN LESIONES HEMORRHAGIC INTRACRANIAL

Es date un description de (1) un caso de hemorrhagia cerebral in le qual un multo alterante aspecto del pigmentos in le liquido spinal permitteva certe deductiones quanto al curso del processo cerebral e (2) un caso de chronic hematoma subdural in le qual le pigmentos del liquido cerebrospinal forniva le diagnose de hematoma.

*) The absorption curve for oxyhaemoglobin has a narrow maximum at 415 nm and that of methaemoglobin at 406 nm. In mixtures the peak assumes an intermediate position. Bilirubin has a wide maximum at 455 nm.

References:

Heilmeyer, L.: Medizinische Spektrophotometrie, Gustav Fischer, Jena 1933, p. 261.

Barrows, L. J., F. T. Hunter & B. Q. Banker: Brain 1955, *78:* 59.

Kronholm, V. & J. Lintrup: Acta Psych. Neurol. Scandinav. 1960, *35:* 314.

PREPARATION OF HUMAN SERUM IN LIQUID FORM FOR INFUSION

By P. EJBY POULSEN

Preparation of dry serum for infusion was started at Statens Seruminstitut, Copenhagen, in 1944. The drying is performed according to the spray drying method.*) A detailed description of this procedure was given by Marcussen in 1945 (8), and since that time it has not been essentially altered.

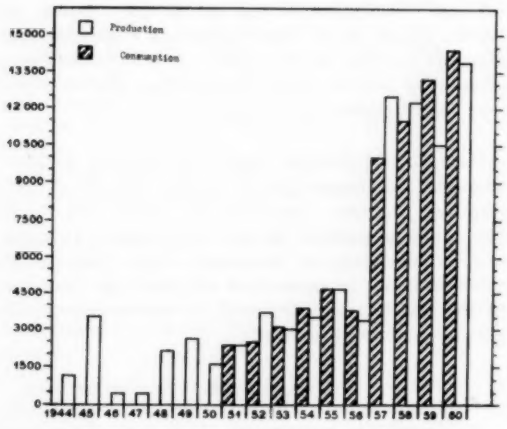


Fig. 1.

The Total Production and Consumption of Dry Serum, Serum and Plasma.

Table I lists the production and dispensing of dry serum, human serum in liquid form, and plasma throughout the years. In Fig. 1 this is presented graphically, the various products for each year being added up. Dry serum in a double portion is calculated as 2 single portions.

It will be seen that apart from the first years, the production of dry serum has remained fairly constant, showing a slight increase up to 1957. During this period, the consumption was evenly increasing, more so than the production which reached a maximum in 1955 when the capacity of our drying plant became fully utilized.

In 1951 there was a particularly great increase in the consumption, because in order to facilitate its use and to reduce the incidence of complications, we had started supplying dry serum in one-litre bottles of Danish Standard accompanied by sterile, apyrogenous water for solution.

Until 1950, dry serum was dispensed in small bottles of 40 g. As these bottles were not accompanied by water, the administration was rather cumbersome, and serum infusion often gave rise to febrile reactions.

In 1951 we also started dispensing bottles holding double the quantity of dry substance, the so-called "double portions". These bottles were accompanied by the usual ½ l of water so that solutions contained a twofold concentration of serum.

In order to keep up with the increasing consumption, we had to alter our production. Since, moreover, the preparation of the various protein fractions in human plasma was in rapid development due to the increasing possibilities of their clinical use, an attempt was made to work out a method for producing liquid plasma from citrated blood. The rate of development of a safe technique for producing plasma, however, could not keep pace with the demand, so that by way of

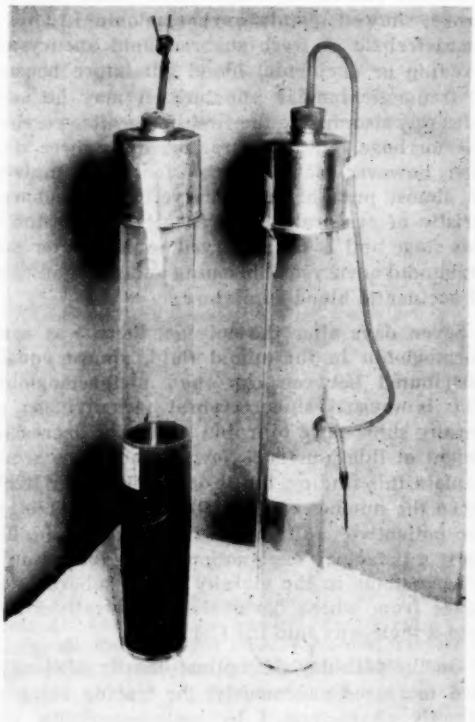


Fig. 2.

Cylinder Glasses for Drawing Blood. On the Left a Cylinder Glass with Blood Which has been Standing for 24 Hours. On the Right a Cylinder Glass Furnished With Rubber Tubing and Needle, Ready for Drawing Blood.

From The Blood Bank, Statens Seruminstitut, Copenhagen.

*) Plant made by Niro Atomizer, Copenhagen.

Table I.

Production and Dispensing of dry Serum and Human Serum from 1945 up to and Including the First half of 1960.

Year	Production				Dispensing			
	Dry serum		Human serum	Plasma	Dry serum		Human serum	Plasma
	1/2 l.	1/1 l.	1/2 l.	1/2 l.	1/2 l.	1/1 l.	1/2 l.	1/2 l.
1944	1107							
1945	3482							
1946	446							
1947	450							
1948	2101							
1949	2602							
1950*)	1511	53						
1951	2082	140			2049	171		
1952	2539	601			1901	331		
1953	2156	392			2234	406		
1954	2414	580			2883	508		
1955	3585	547			3358	662		
1956	2607	444			2797	509		
1957	17	1821	8820			1262	7433	
1958		1167	9135	778**)		1076	9102	234
1959		612	6736	2530		751	9166	2496
1/1—30/6 1960			4361	2577		200	3762	3034

*) At this time standard bottles and double portions were introduced.
**) Production of plasma was started in May 1958.

transition we had to introduce the manufacturing of human serum in the liquid form.

The production of plasma is now rapidly progressing, but for various technical reasons the serum production is being continued, and it is the latter which will be described in the present publication. A report of the plasma prouction will appear in a subsequent paper.

As apparent from Table I, the production of dry serum was almost completely discontinued in 1957. Only the drying of serum used for "double portions" is still being carried out.

Human serum in liquid form possesses the following advantages above dry serum:

(1) Easier to produce,
(2) easier to administer,
(3) less risk of hepatitis,
(4) no denaturation of proteins,
(5) requires less storage space.

The production of human serum for infusion is carried out in the following steps:

BLEEDING

We use blood from volunteer donors between 18 and 65 years of age. Blood from 3—4 donors is used for preparing half a litre of serum.

Before being bled, the donors are asked whether they have been jaundiced. Blood from donors who have had jaundice is not used for preparing serum, but is drawn as citrated blood and used for fractionation.

The blood is drawn into tall cylinder glasses with an aluminium cap reaching some cm down the sides (Fig. 2). The tubing is fixed through a rubber stopper in the lid and at the other end it is fitted with a hyprodermic needle. The method is simple and completely excludes the risk of air embolus in the donor. Moreover, the risk of contaminating the blood has proved negligible.

Immediately after drawing the blood, the tubing is folded double close to the stopper, closed with at paper clip, and cut.

Special blood samples, *e. g.* for blood grouping, are drawn from the donor after cutting the tubing.

Immediately after the procedure, the glass is placed in the refrigerator and left at 4° C overnight.

FILTRATION OF THE BLOOD

The contents of the glasses are emptied into a coarse filter (Fig. 3) consisting of a bucket of stainless steel with an oblique bottom and a tap placed above the highest part of the bottom. In-

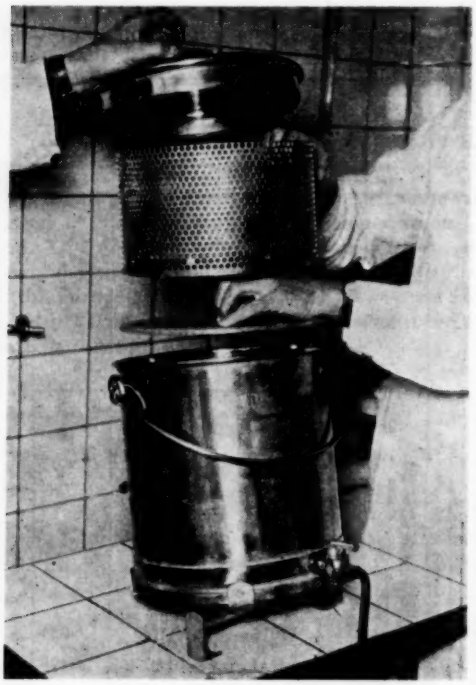


Fig. 3.

Coarse Filter. Consisting of a Bucket of Stainless Steel with a Lid, Filter Insert, and Tap. The Bucket is Placed on a Stand Which may be Tilted by a Screw Device.

side the bucket is a filter insert calibrated so as to retain larger clots, but allowing small clots and "loose red cells" to pass. This is done so that the erythrocytes may absorb the isoantibodies from the serum.

The filter is placed obliquely on a tilting device, so that the red cells may settle in the deeper part of the oblique bottom, and so that in tapping the serum the filter may be tilted into the horizontal position so that all the serum may be tapped off.

Each filter will hold blood from 25—30 donors.

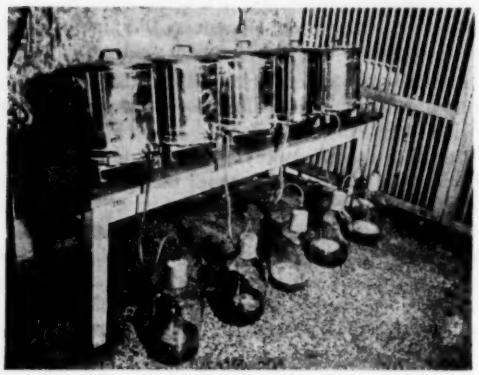


Fig. 4.

Bottling From Coarse Filters After Standing for 2 Days at 4° C.

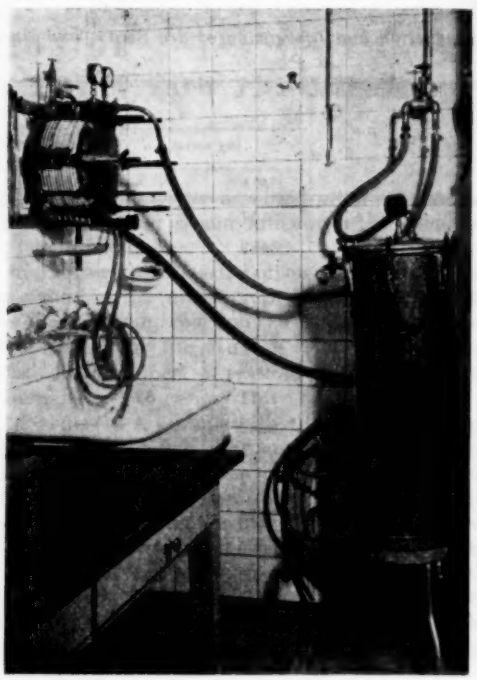


Fig. 5.

Sterile Filtration. On the Right a Pressure Tank. On the Left Zeiss Filter Furnished with 12 EKS Filter Discs.

After standing for 2 days, at 4°C, the serum is drawn off. It is now almost clear and free of erythrocytes (Fig. 4). It is immediately poured nto a pressure tank from where it is passed through a Zeiss filter (E. K. S.) which retains the erythrocytes and bacteria, if any (Fig. 5). The filtration has to be done at low pressure in order not to crush the erythrocytes.

The procedure is planned so that only 3 days elapse from drawing the blood until the sterile filtration of the serum. During this period the blood is stored at 4°C in order to prevent major growth of bacteria. After the serum has been Zeiss filtered, it is ready for storage.

STORING THE SERUM

Previously, serum was placed at —15°C for about 3 months, but it has proved easier and just as safe to keep it at room temperature. In that case, it is stored only for 3 weeks. In the course of storage, remains of fibrinogen will sediment, so that after the final filtration, the serum is clear and stable.

In addition, storage inactivates substances which induce anaphylactic shock in rabbits, and which prevent pyrogen testing of the serum

BOTTLING

After storage for 2—3 weeks, according to the procedure, the serum is bottled in half-litre

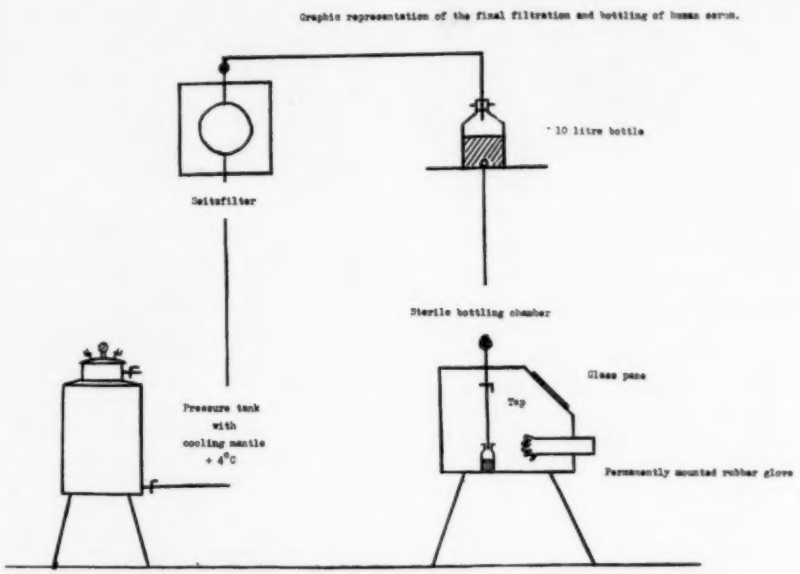


Fig. 6.
Graphic Representation of the Final Filtration and Bottling of Human Serum.

bottles*), as shown in Fig. 6. The serum is pressed from a pressure tank where it is kept refrigerated at 4°C, through Zeiss filters into a 10 l bottle. Hence it is allowed to drip into the closed bottling chamber shown on Fig. 7. The bottling procedure is handled under aseptic conditions by means of built-in rubber gloves, and the bottles are stoppered in the closed chamber.

The entire system containing empty bottles and stoppers is steam sterilized at the same time so that there is no possibility of contamination during the bottling procedure.

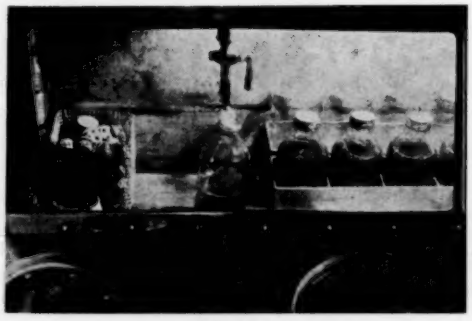


Fig. 7.
Bottling into Half-litre Bottles. Through the Glass Pane the Bottling Chamber and the Tap may be seen. On the Right Filled and Stoppered Bottles. On the Left a Basket with Rubber Stoppers. At the Bottom the Built-in Gloves by Means of which the Tapping is Carried out.

*) Danish Standard.

After the tapping into half-litre bottles, the bottles are labelled with date of bottling and number, so that they can be traced to the pool from which the serum was derived and thereby to the donors whose blood was used for the preparation.

STORAGE

The serum is then stored at room temperature in order to inactivate hepatitis virus, if present.

The risk of transmitting hepatitis virus, leading to serum hepatitis, has been and still is a problem in all preparations made from human blood.

According to S. Madsen (7) dry serum gives rise to hepatitis in 2—3 per cent of the recipients. Kjærgård (6) demonstrated that irradiation with ultraviolet light does not alter the incidence as is also apparent from American investigations by Albrecht et al. (1).

Allen et al. (2), storing serum at room temperature, found that storage at this temperature for six months inactivated hepatitis virus. This was later confirmed by Hoxworth et al. (4 and 5) in experiments on blood from patients with hepatitis.

In preparing human serum, therefore, a storage period of six months is preferable. Regrettably, this cannot be attained in all cases. After shorter storage, the incidence of hepatitis is at least lower than the 2—3 per cent seen with dry serum, falling evenly in the course of the time that the serum is stored.

As evident from Table I we have dispensed a total of 29,052 portions of human serum up to

July 1960 and only one case of serum hepatitis has been reported.

During the storage, the following tests are performed:

CONTROL TESTS

sterility test
pyrogen test
test for haemoglobin content
test for sodium and potassium content
test of anti-A and anti-B in saline solution
test for immune anti-A and anti-B.

Sterility test.

The sterility test is carried out by the control department of the Statens Seruminstitut (Head: M. Volkert, M. D.). For this test, we use the last serum remaining in the feed tank (Fig. 7) after the tapping.

Pyrogen test.

This test for pyrogens in the serum is carried out on rabbits. Quite fresh serum kills rabbits which succumb showing signs of anaphylactic shock. This effect is reduced by storage, so that only a few of the rabbits in a series die, while others show a fall of temperature. Not until the serum has been stored for 2—3 weeks at room temperature or for 2—3 months at —20°C has this action disappeared, and not until then can the serum be studied for pyrogenicity.

The pyrogen test is carried out on five male rabbits weighing about two kg which have not been used for experiments previously. By a rectal thermometer, the morning temperature is taken. If it is within the range of normal, 20 ml of serum is injected into an ear vein. The rabbits are placed in separate cages, and their temperature are taken hourly, a total of three times.

The test is considered positive if two or more rabbits show an elevation of temperature of 0.6°C or more or if the average elevation of temperature exceeds 0.5°C. (E. Fullerton Cock, 3).

As a rule, the rabbits show an average elevation of between 0.1° and 0.3°C. If they show a fall of temperature, as mentioned above, this is a sign that the serum has not been stored for a sufficient length of time. Pyrogenic serum can usually be cleared of pyrogens by freezing for three months and renewed filtration (Herbert Wilke (12)).

Test for haemoglobin content.

The U. S. A. Minimum Requirements from 1952 (10) prescribe that the haemoglobin content in plasma must no exceed 25 mg per 100 ml. We used the method described here until March 1956, when we adopted a method advocated by McCall (9) based on spectrophotometric measurements at 540 μ in serum whose haemoglobin had been converted partly to methaemoglobin and partly to cyanmethaemoglobin.*)

In practice, it was gradually found that clear, not red-coloured serum contains far less than 25 mg haemoglobin per 100 ml. Thereafter, we omitted the determination as a routine, doing it only in cases of doubt.

Tests for sodium and potassium content.

These tests were introduced recently at the request of the clinicians. They are carried out by flame photometry on each pool. The sodium and potassium levels in human serum in liquid form correspond approximately to the normal serum levels, but with a tendency to a slightly higher potassium content. These determinations have been performed on the last 29 pools. The sodium level varies from 120 mEq/l to 147 mEq/l, and the potassium level ranges from 3.6 mEq/l to 6.3 mEq/l.

Test for anti-A and anti-B.

A sample from each lot is titrated with A and B blood cells. Mixing the blood of 25—30 random donors and storing it for up to six months, we have in almost all instances been able to keep the titre below 1/8.

Sera having very high titres, 1/32 or over, are stored for another 3 months and re-filtered. Thereby, we have always obtained a suitable fall in the titre.

Test for immune anti-A and anti-B.

Tests were carried out by the dextran technique as described by G. Munk-Andersen (11). As a rule the titre is about 1/32. Sera with a very high titre are stored and refiltered.

PACKING AND STORING

If the tests described above are all satisfactory, the bottled serum is packed into cartons labelled with the number of the pool, and it is now ready to be dispensed with instructions that it has to be stored at room temperature (Fig. 8).

The finished product, called "Human serum", is as close as possible to fresh normal serum. Its protein content is between six and seven per cent and it shows a normal electrophoretic curve. It is sterile and apyrogenic. The only disadvantage is the risk of hepatitis, but this risk is very slight. In addition, there is a theoretical risk of haemolytic reaction due to anti-A and anti-B content upon repeated infusions. This risk too is very slight.

Each bottle is accompanied by a card to be returned with reports of complications, if any. Judging by these cards, the incidence of complications is low, less than 2.3 per cent.

---

*) Determinations carried out by V. Møller, Ph. D.

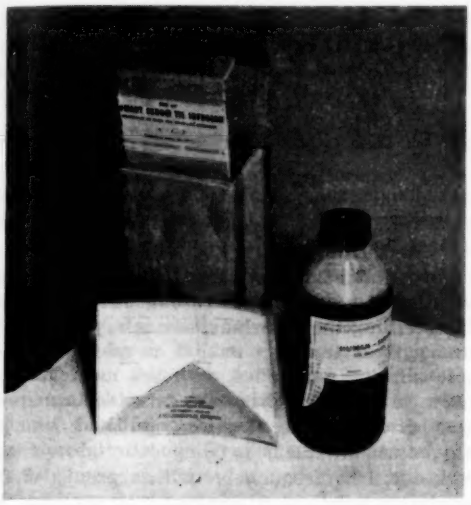


Fig. 8.
Half a Litre of Human Serum for Infusion Ready for Use.

The serum is stable for at least 5 years — and probably much longer if stored under proper conditions.

The indications for its use are as follows:

(1) Shock of any kind.
(2) Hypoproteinaemia.
(3) For parenteral nutrition.

SUMMARY

The increasing use of dry serum necessitated a change in the production to a more efficient method. The aim was to prepare human plasma in liquid form. As a transitional link, we prepared human serum in liquid form which possesses the following advantages over dry serum:

(1) Easier to prepare
(2) easier to administer
(3) less risk of hepatitis
(4) no denaturation of proteins
(5) less storage space required.

The preparation consists in filtration, storage and bottling.

Tests are made for sterility, pyrogenicity, haemoglobin content, sodium and potassium content, and for anti-A and anti-B content in saline medium and in dextran.

Serum is stored as far as possible for 6 months at room temperature in order to inactivate hepatitis virus, if present.

The serum has a protein content of 6—7 per cent and a normal electrophoretic curve.

It seldom gives rise to reactions and is considered to be stable for at least 5 years. The demand is steadily increasing.

SUMMARIO

Ejby Poulsen: PREPARATION DE SERO HUMAN PRO INFUSION

Le uso de plus in plus frequente de sero sic necessitava un cambiamento de production verso un methodo plus efficace. Le scopo esseva le preparation de plasma human in forma liquide. Como passo transitional nos preparava sero human in forma liquide, lo qual possede le avantages sequente super sero sic:

(1) Plus facile a preparar.
(2) Plus facile a administrar.
(3) Minor risco de hepatitis.
(4) Nulle denaturation de proteinas.
(5) Minor spatio de deposito requirite.

Le acto del preparation consiste in le filtrar, le stockar e le imbottiliar.

Es executate tests de sterilitate, pyrogenicitate, contento de hemoglobina, contento de natrium e kalium, e contento de anti-A e anti-B in medio salin e in dextrano.

Quanto possibile le sero es stockate durante 6 menses a temperatura de camera a fin de inactivar un virus de hepatitis eventual.

Le sero ha un contento de proteina de 6—7 per cento e un curva electrophoretic normal.

Illo rarmente causa reactiones, e illo es tenite pro stabilisate indefinitemente. Le requesta augmenta constantemente.

References:

1) *Albrecht, Robert M., R. F. Korns, W. G. Beadenkopf, M. B. Goodman, F. B. Locke & V. Marks:* JAMA 1953, *152:* 1423.
2) *Allen, J. G., D. M. Enerson, E. S. G. Barron & C. Sykes:* JAMA 1954, *154:* 103.
3) *Cock, E. Fullerton:* Pyrogen Tests. Expert Committee on the Unification of Pharmacopoeias. 1950, (WHO, Pharm/116).
4) *Hoxworth, Paul I. & C. E. Haesler jr.:* Annals of Surgery 1956, *144:* 336.
5) *Hoxworth, Paul I. & C. E. Haesler jr.:* JAMA 1958, *166:* 1291.
6) *Kjærgaard, Gunnar:* Ugeskr. Læger 1950, *112:* 1014.
7) *Madsen, Sten:* Ugeskr. Læger 1954, *116:* 637.
8) *Marcussen, Poul V.:* Ugeskr. Læger 1945, *13:* 263.
9) *McCall, K. B.:* Analytical Chemistry 1956, *28:* 189.
10) Minimum Requirements: Normal Human Plasma. National Institutes of Health, 9th. revision, 1952.
11) *Munk-Andersen, Georg:* Haemolytic Disease of the Newborn due to ABO Incompatibility. København 1959.
12) *Wilke, Herbert:* Pharm.ind. 1953, *15:* 224.

THE SICKNESS SURVEY OF DENMARK

A SUMMARY

By POUL BECHGAARD, N. S. JACOBSEN & MARIE LINDHARDT

With the object of ascertaining the morbidity and the nature of the sicknesses occurring among the Danish people, the Sickness Survey was started on May 1, 1951 and lasted until April, 1954.

Defining the sickness was left to the respondents themselves: If I feel ill, I am ill. The survey was to comprise 3 per cent of the adult population, *i. e.* about 100,000, who were to be questioned about the state of their health during the previous month by specially trained interviewers armed with a questionnaire.

Until now there has been but few surveys of this kind. Early in the 20th century the methods of rational procedure in the securing of morbidity statistics began to take shape. Among the British pioneers were Charles Booth, who assembled information concerning sickness and other social matters among families in no fewer than 3,400 streets of London, and Rowntree, who in 1899 began a morbidity survey in the city of York. His particular merit was that he introduced the method of asking people directly without using intermediaries to procure information.

In 1924 Sydenstricker, U. S. A., made his classical Hagerstown survey, where for 28 months he followed 9,000 persons, one third of the population of the city.

Since the war five states are known to have completed or at any rate commenced nation-wide surveys of this kind: Great Britain (1943—52), Japan (1948—), Canada (1950—51), Denmark (1951—54) and U. S. A. (1957—) but the methods employed, all founded upon careful preparation, are nevertheless so different that comparisons of the results are simply out of the question. The explanation may be chiefly the impossibility of defining the concept of sickness: when does a sickness begin, when does it end? The transition from the commencement of a sickness to its termination in cure or death embraces so many phases that exact numerical expressions fail.

It was with their eyes fully open to these circumstances that the *Committee on the Danish National Morbidity Survey* accomplished its extensive investigation of the morbidity in Denmark. The results obtained are announced with the reserve that is traditional but necessary in medical statistics.

A broad and fairly representative sample of the entire adult population have had an opportunity of describing their various ailments, and for the most part it turned out that people's ideas of these ailments coincided with the medical diagnoses. As a result it has been possible to map all these diseases and morbid conditions numerically, assemble them in diagnostic groups and work out their frequencies within groups of the population subdivided according to sex, age, residence etc.

METHODS

The methods of the study are described in details in the report of the committee. 100,000 persons of more than 15 years, forming 3 per cent of the adult population, were picked out at random, but in such a way that they made a representative group of the population. Of the selected persons the survey failed to contact 17 per cent, but merely 1.6 per cent of those contacted directly refused to participate.

The thoroughly planned *questionnaires* were filled in by 165 specially trained interviewers who visited the selected persons in their homes. The interviewer opened the conversation by asking, if the respondent had suffered from any illness or met with any accident during the previous month.

The mechanical analysis was made on punch card machines. To code the diseases, which were grouped according to a specially compiled list of diagnoses, double coding was employed by two trained codifiers, the result being that the divergence between them was 2.7 per cent.

In order to have some sort of check on the layman *diagnoses* the doctors were asked to fill in a control questionnaire containing the name and address of the particular patient as well as the ailment or ailments stated by the patient to the interviewer.

Of the persons who had consulted their doctor within the stated period 40 per cent had their diagnosis corrected or supplemented by the doctor. In 71 per cent of the cases there was complete agreement between the doctor and the patient as to diagnosis, in 16.3 per cent the doctor knew nothing of the case, in 6.5 per cent he added an additional disease, and in only 6.2 per cent there was apparently a direct disagreement between doctor and patient.

The Sickness Survey of Denmark. Munksgaard, Copenhagen 1960, 262 pp. Published by the Committee on the Danish National Morbidity Survey. Text by Marie Lindhardt.

From The National Health Service of Denmark, Copenhagen.

Funds were procured through support from the Rockefeller Foundation, the Danish State and various Danish financial institutions.

The results of previous statistical investigations regarding the occurrence of pulmonary tuberculosis, diabetes and gastric ulcer agree very well with those of the Sickness Survey.

RESULTS

Up to the age of 60 some difference in the morbidity in relation to the *marital state* can be seen. Single persons of almost all ages and of both sexes have a slightly lower morbidity than married and separated persons, whereas divorcees and persons in the widowed state have the highest morbidity, especially in the younger years.

Concentrating on the *main occupational groups* it would seem that occupation has no great influence on the total morbidity. The higher morbidity of females applies to both self-employed women and those at home. A subdivision of the material into self-employed, salaried employees and wage-earners shows in the main: almost everywhere the employee class has the lowest morbidity, wage-earners the highest, especially among the elderly ones. This applies solely to males. Most accidents happen among the working class, and there are most nervous complaints and colds in the employee class.

Among a grand total of 86,788 respondents 35,824 persons were ascertained to have had 53,733 illnesses, including 1,147 accidents. The total morbidity in the sense of sick persons in relation to all respondents (the international "sickness rate") is thus 41.3 per cent. For males the rate is 35.6, for females 46.9 per cent. The number of diagnoses per sick person was 1.49, *i.e.*, 1.38 for males and 1.59 for females. The morbidity rises steadily with the age and is higher among females everywhere, see Figure 1. Between the four main sections of the country the differences in the morbidity are small. The so-called built-up areas in the provinces seem to have the lowest morbidity.

The disease with the highest frequency in both sexes is the common cold. This is followed among males by: muscular pain (rheumatism), chronic bronchitis etc., gastro-intestinal ailments and influenza. Among females the series is: menstrual disorders and other women's complaints, muscular pain, nervous diseases and chronic bronchitis etc. This order changes when a distinction is made between the age classes, see Table I where each single diagnosis is given per 1,000 respondents by sex and age, and total diagnoses and respondents in absolute figures.

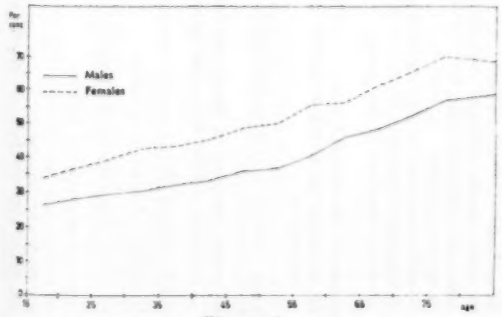


Figure 1.

Sickness Rates by Sex and Age in Whole Country 1951—54. Sick Persons per 100 of all Respondents.

In a general table employing 19 diagnosis groups a comparison is made between 1) *home morbidity* (Sickness Survey), 2) *hospital admissions* (Hospital Survey) and 3) *Causes of Death* (the official regular statistics), drawn up as monthly averages and distributed as to sex and age, see Table II.

The values on which these figures are based are highly unequal in magnitude: every year about 40,000 adult people die in Denmark; admissions to the medical-surgical hospitals on which the Hospital Survey is based number about 300,000 per annum, and the number of illnesses in the homes reaches over a million per month. Accordingly the position is best illustrated by means of a relative distribution of these unequal values (see Figure 2). The graphs visualize the shares of the 19 groups of diagnoses in all illnesses. As indicating the utility of these comparisons it may perhaps be pointed out that the figures provide a guide for the medical profession as to what forms of sickness they will most often have to deal with in general practice and in hospital.

The figures in the comparison must be evaluated with reserve — a drawback often inherent in medical statistics. As regards both "home" and "hospital" sicknesses it will be observed that the Survey does not take cognizance of their duration. For example, the figures in Figure 2 for a group such as neoplasms, comprising a great majority of malignant cases (cancer), are relatively low for "home" sickness, much higher for hospitalized patients and highest of all for the deaths, whereas the reverse is the case for colds; but it must be remembered that the former group comprises protracted, chronic diseases and the latter acute diseases of but few days' duration.

Accidents are relatively rare among the reported cases of sickness, of which they represent only 1,147: 723 among males and 424 among females, in all about 2 per cent of the total. Traffic accidents figure to the extent of 13 per cent. Per 1,000 respondents the accident rate was 16.8 for males, 9.7 for females and for both sexes 13.2. For males the frequency was highest in the age group 15—39 years: 18.6 per 1,000, and for females over 60 years: 15.2 per 1,000.

Meteorological conditions seem to have had little influence on the total morbidity. The only connection observable is for affections of the respiratory organs, i.e. more sickness in winter than in the other seasons. There is a trend towards high temperature and low humidity giving

Table I.

Distribution of Diagnoses (85 Numbers Among all Respondents per 1,000 Persons by Sex and Age. 1951—54.

Diagnoses	Males				Females				Both sexes			
	15—39 years	40—59 years	60 years and over	15 years and over	15—39 years	40—59 years	60 years and over	15 years and over	15—39 years	40—59 years	60 years and over	15 years and over
A. Infectious diseases												
a. tuberculosis												
01 tuberculosis of the respiratory system	2.6	2.0	0.5	2.0	2.7	1.4	1.1	2.0	2.7	1.7	0.8	2.0
02 tuberculosis, other forms	0.2	0.5	0.3	0.3	0.8	1.0	0.9	0.9	0.5	0.7	0.6	0,6
b. other infectious diseases												
03 late effects of acute poliomyelitis	1.0	1.0	0.4	0.9	1.4	1.2	0.3	1.2	1.2	1.2	0.3	1.1
04 dermatophytosis	3.5	0.7	0.5	2.0	1.2	1.0	0.7	1.1	2.3	0.9	0.6	1.5
05 acute infectious and epidemic gastro-intestinal diseases	6.3	6.0	3.5	5.7	6.2	4.9	4.8	5.5	6.2	5.5	4.1	5.6
06 other infectious or epidemic diseases	2.0	0.9	2.7	1.7	2.1	2.3	3.8	2.5	2.0	1.6	3.2	2.1
B. Neoplasms												
07 malignant and benign neoplasms	0.4	1.8	4.4	1.6	3.1	7.3	6.3	5.1	1.8	4.5	5.4	3.4
C. Allergic diseases, metabolic diseases etc.												
a. allergic diseases												
08 asthma	3.5	9.0	15.4	7.5	3.4	7.4	11.8	6.2	3.5	8.2	13.6	6.9
09 other acute allergic disorders	1.5	1.1	0.8	1.3	2.3	2.9	1.3	2.3	1.9	2.0	1.1	1.8
b. metabolic disorders etc.												
10 thyrotoxicosis	—	0.3	0.3	0.2	1.2	2.8	3.1	2.1	0.6	1.5	1.7	1.1
11 other diseases of the thyroid gland	0.3	0.1	—	0.2	1.6	2.6	2.2	2.0	0.9	1.4	1.1	1.1
12 diabetes mellitus	1.5	3.7	10.1	3.8	1.8	6.2	20.6	6.5	1.7	4.9	15.3	5.2
13 other diseases of the group	0.6	1.3	1.7	1.1	2.7	4.1	3.9	3.4	1.7	2.7	2.8	2.2
D. Diseases of the blood												
14 anaemia and other blood diseases except malignant	0.9	1.2	3.7	1.5	7.1	5.0	10.2	6.9	4.1	3.1	7.0	4.2
E. Nervous disorders and mental diseases												
15 nervous heart	1.6	4.0	3.2	2.8	5.8	10.5	7.4	7.7	3.8	7.2	5.3	5.3
16 other diseases of the group incl. organic and psychoneurotic and general nervousness ..	8.4	14.6	12.5	11.4	22.9	39.0	34.3	30.4	15.9	26.6	23.3	20.9
F. Vascular lesions of the central nervous system												
17 apoplexy	0.1	0.9	6.0	1.4	0.5	0.7	7.5	1.8	0.3	0.8	6.8	1.6
18 sciatica	3.5	12.8	11.2	8.1	3.2	9.1	11.4	6.6	3.3	11.0	11.3	7.4
19 other diseases of the group	3.4	6.7	12.4	6.1	5.8	11.9	15.1	9.5	4.6	9.3	13.7	7.8
G. Diseases of the eye												
20 inflammation	7.5	8.9	11.2	8.6	9.2	13.2	19.9	12.4	8.4	11.0	15.5	10.6
21 impaired vision	4.1	8.3	23.0	8.9	5.8	11.0	39.3	13.3	5.0	9.6	31.1	11.1
22 other and ill-defined diseases of the eye ..	2.1	2.3	5.2	2.7	2.5	5.1	7.4	4.2	2.3	3.7	6.3	3.5
H. Diseases of the ear												
26 rheumatic fever and rheumatic heart diseases	0.9	1.5	0.9	1.1	1.1	2.3	1.9	1.6	1.0	1.9	1.4	1.4
27 degenerative and arteriosclerotic heart dis-												

20 inflammation	7.5	8.9	11.2	8.6	9.2	13.2	19.9	12.4	8.4	11.0	15.5	10.6
21 impaired vision	4.1	8.3	23.0	8.9	5.8	11.0	39.3	13.3	5.0	9.6	31.1	11.1
22 other and ill-defined diseases of the eye	2.1	2.3	5.2	2.7	2.5	5.1	7.4	4.2	2.3	3.7	6.3	3.5
H. Diseases of the ear												
26 rheumatic fever and rheumatic heart diseases	0.9	1.5	0.9	1.1	1.1	2.3	1.9	1.6	1.0	1.9	1.4	1.4
27 degenerative and arteriosclerotic heart diseases	0.8	7.3	55.9	12.7	0.8	11.0	74.8	16.9	0.8	9.1	65.3	14.8
28 other and ill-defined diseases of the heart	2.6	8.3	13.2	6.5	3.7	10.5	17.5	8.4	3.2	9.4	15.3	7.4
b. hypertensive heart disease												
29 hypertension with heart disease	0.1	0.7	4.5	1.1	0.2	2.6	13.2	3.3	0.1	1.6	8.8	2.2
30 hypertension without heart disease	0.3	1.7	4.9	1.6	0.4	6.2	21.9	6.1	0.4	3.9	13.4	3.9
c. diseased arteries and veins												
31 general arteriosclerosis	0.1	0.7	24.0	4.4	—	0.7	27.0	4.8	0.1	0.7	25.5	4.6
32 haemorrhoids	1.3	1.6	1.3	1.4	1.5	1.9	0.8	1.5	1.4	1.7	1.1	1.5
33 varicose veins, phlebitis, skin lesions	3.8	12.9	13.3	8.7	14.4	34.1	38.5	25.3	9.2	23.4	25.8	17.0
34 other diseases of the group	0.3	1.0	1.5	0.7	0.3	1.0	2.3	0.9	0.3	1.0	1.9	0.8
K. Diseases of the respiratory system												
a. acute disorders in upper air passages, and pneumonia												
35 colds, catarrh, pyrexia	87.1	68.5	65.5	76.7	76.1	58.7	57.5	67.0	81.5	63.7	61.5	71.8
36 other acute infections of upper air passages	18.4	13.7	14.1	16.0	24.5	20.9	23.1	23.0	21.5	17.2	18.6	19.5
37 influenza	17.4	18.4	18.8	18.0	21.6	24.7	27.6	23.7	19.6	21.5	23.1	20.9
38 pneumonia	0.9	1.2	4.4	1.6	1.4	1.6	4.0	1.9	1.2	1.4	4.2	1.8
b. chronic diseases in upper air passages												
39 chronic bronchitis and other chronic infections of upper air passages	18.0	32.0	48.5	28.3	18.4	36.1	52.2	30.3	18.2	34.0	50.3	29.3
c. other diseases in lungs and pleura												
40 pleurisy, non-tuberculous	0.4	0.6	0.9	0.6	0.5	0.4	0.3	0.4	0.4	0.5	0.6	0.5
41 other pulmonal diseases	0.9	4.6	7.6	3.4	0.7	1.9	1.7	1.3	0.8	3.2	4.7	2.3
L. Diseases of the digestive system												
a. diseases in oral cavity, throat and gullet												
42 toothache and dental diseases	10.5	9.0	6.5	9.3	12.4	6.9	2.4	8.8	11.5	7.9	4.5	9.0
43 other diseases of the group	1.4	1.8	2.4	1.7	3.1	3.9	6.2	3.9	2.3	2.8	4.3	2.8
b. diseases in stomach and duodenum												
44 gastric and duodenal ulcer	8.4	17.6	14.6	12.7	2.8	7.3	7.3	5.1	5.5	12.5	11.0	8.9
45 other diseases of the group	21.3	29.1	25.4	24.8	12.4	16.5	25.1	15.9	16.7	22.9	25.3	20.3
c. diseases of the appendix												
46 appendicitis	1.4	0.8	0.5	1.0	1.3	1.1	0.8	1.1	1.3	0.9	0.7	1.1
d. hernia												
47 hernia, all forms	1.6	3.0	10.0	3.6	0.3	1.9	4.8	1.6	1.0	2.5	7.4	2.6
e. other intestinal disorders												
48 constipation	2.0	3.0	10.5	3.8	5.4	8.8	11.4	7.6	3.7	5.9	11.0	5.7
49 other diseases of the group	5.5	9.3	13.6	8.3	9.3	15.9	20.2	13.4	7.4	12.5	16.9	10.9
f. diseases of biliary ducts and liver etc												
50 gallstone and other disorders of biliary ducts	0.7	3.3	4.8	2.4	7.4	24.8	26.8	16.7	4.1	13.9	15.7	9.6
51 diseases in liver and pancreas	0.6	0.5	0.5	0.5	0.3	0.7	1.3	0.6	0.5	0.6	0.9	0.6
M. Diseases of kidneys, urinary system and male genitals												
52 nephritis and pyelitis	0.5	0.9	1.1	0.7	3.0	3.0	4.2	3.2	1.8	1.9	2.6	2.0
53 calculi	1.3	2.7	2.7	2.0	0.8	2.6	2.2	1.6	1.0	2.7	2.4	1.8
54 diseases of bladder	0.9	1.4	8.3	2.4	5.7	7.3	15.9	8.0	3.4	4.4	12.0	5.2
55 other diseases of the group	1.3	3.5	21.4	5.6	2.4	4.3	9.1	4.2	1.8	4.0	15.3	4.9

Diagnoses	Males				Females				Both sexes			
	15–39 years	40–59 years	60 years and over	15 years and over	15–39 years	40–59 years	60 years and over	15 years and over	15–39 years	40–59 years	60 years and over	15 years and over
N. Women's complaints												
56 diseases of the breast (excl. cancer)	.	.	.	.	0.6	0.3	—	0.4	0.3	0.1	—	0.2
57 inflammation of internal genitals etc.	.	.	.	.	33.4	16.2	18.4	24.9	17.1	8.0	9.2	12.5
58 disorders of menstruation	.	.	.	.	78.9	19.9	0.1	45.2	40.4	9.8	0.1	22.8
59 menopausal symptoms (incl. menstrual irregularities)	.	.	.	.	1.0	65.4	0.8	23.1	0.5	32.3	0.4	11.6
60 complications of pregnancy, abortion, childbirth and sequelae	.	.	.	.	11.1	0.8	0.1	5.7	5.7	0.4	0.1	2.9
O. Skin diseases												
61 "swollen finger" etc.	5.7	4.5	2.8	4.8	2.7	2.3	2.7	2.6	4.2	3.5	2.7	3.7
62 skin eruption	10.1	12.3	14.5	11.7	14.5	16.4	17.3	15.6	12.3	14.3	15.9	13.7
63 psoriasis	0.6	1.3	0.5	0.9	0.8	0.9	0.7	0.8	0.7	1.1	0.6	0.8
64 other diseases of the group	4.8	2.9	3.9	4.0	5.0	4.9	4.8	4.9	4.9	3.9	4.3	4.4
P. Diseases of bones, joints and muscles												
a. rheumatic diseases												
65 arthritis	1.0	6.6	15.6	5.5	3.4	21.0	44.1	16.3	2.2	13.7	29.8	11.0
66 arthrosis	0.4	6.6	24.1	6.7	0.3	11.7	39.5	10.9	0.3	9.1	31.8	8.8
67 lumbago	4.4	9.6	6.1	6.6	3.3	5.9	6.0	4.7	3.9	7.8	6.1	5.6
68 muscular pain	11.8	36.2	73.8	31.2	16.2	55.3	103.8	44.5	14.0	45.6	88.7	37.9
b. other diseases												
69 other diseases of bones, joints and tendons	10.4	10.6	11.8	10.7	10.8	13.7	14.9	12.5	10.6	12.1	13.4	11.6
70 deformities of the feet	3.4	2.8	2.8	3.1	6.3	8.1	7.7	7.1	4.8	5.4	5.2	5.1
71 other deformities of bones	1.2	1.9	2.7	1.7	0.6	2.4	5.0	2.0	0.9	2.1	3.8	1.8
R. Other diseases												
74 tender feet, swollen legs, defective blood circulation	6.4	9.1	18.9	9.5	15.8	28.1	35.9	23.5	11.2	18.5	27.4	16.5
75 diarrhoea	0.9	0.6	1.3	0.9	0.2	0.5	1.9	0.6	0.6	0.5	1.6	0.7
76 debility, lassitude, run down	2.5	3.6	3.1	3.0	6.0	7.9	6.2	6.7	4.3	5.7	4.6	4.8
77 headache, migraine	8.6	8.3	5.8	8.0	18.0	21.6	11.0	18.1	13.4	14.9	8.4	13.1
78 other and ill-defined diseases	1.2	2.4	3.5	2.0	2.4	2.4	3.6	2.6	1.8	2.4	3.5	2.3
All illness	353.1	489.6	771.1	474.5	570.1	796.0	1087.2	735.8	464.1	640.8	928.4	605.9
80 fracture of skull	0.2	0.3	—	0.2	—	0.1	—	0.0	0.1	0.2	—	0.1
81 fracture of spine and trunk	0.7	1.9	1.9	1.3	0.2	0.6	1.5	0.6	0.5	1.3	1.7	0.9
82 fracture of limbs	2.3	2.4	3.7	2.6	0.6	1.3	3.9	1.4	1.5	1.9	3.8	2.0
83 dislocations, sprains and strains	4.4	4.3	2.8	4.1	2.3	3.5	4.3	3.0	3.3	3.9	3.5	3.6
84 injury of head, chest, abdomen and pelvis	2.0	1.3	1.3	1.6	1.2	1.3	1.7	1.4	1.6	1.3	1.5	1.5
85 laceration and open wounds	4.6	3.4	0.5	3.5	1.9	1.1	0.4	1.3	3.2	2.3	0.5	2.4
86 burns	0.9	—	0.2	0.5	0.5	0.5	0.7	0.5	0.7	0.2	0.4	0.5
87 effects of poison	0.3	0.1	0.2	0.2	0.1	0.1	—	0.1	0.2	0.1	0.1	0.1
88 other effects of external causes	3.2	2.7	2.1	2.8	0.8	1.5	2.7	1.4	1.9	2.1	2.4	2.1
All accidents	18.6	16.4	12.7	16.8	7.6	10.0	15.2	9.7	13.0	13.3	13.9	13.2
Total number of illnesses	7151	7528	5792	20471	12101	11927	8087	32115	19252	19455	13879	52586
" " " accidents	376	252	95	723	161	150	113	424	537	402	208	1147
Altogether illnesses and accidents	7527	7780	5887	21194	12262	12077	8200	32539	19789	19857	14087	53733
Total persons with illnesses or accidents	5980	5599	3787	15366	8405	7412	4641	20458	14385	13011	8428	35824
" " without illnesses or accidents	14273	9777	3724	27774	12822	7571	2797	23190	27095	17348	6521	50964
Total respondents	20253	15376	7511	43140	21227	14983	7438	43648	41480	30359	14949	86788

Morbidity and Mortality on an Average per Month 1951—54. By Diagnoses, Sex and Age.

Altogether illnesses and accidents	7527	7780	5887	21194	12262	12077	8200	32539	19789	19857	14087	53733	
Total persons with illnesses or accidents	5980	5599	3787	15366	8405	7412	4641	20458	14385	13011	8428	35824	
" " without illnesses or accidents	14273	9777	3724	27774	12822	7571	2797	23190	27095	17348	6521	50964	
Total respondents	20253	15376	7511	43140	21227	14983	7438	43648	41480	30359	14949	86788	

Morbidity and Mortality on an Average per Month 1951—54. By Diagnoses, Sex and Age.

No.		Illnesses per month per 1000 respondents				Hospital admissions per month per 100.000 population				Deaths per month per 100.000 population				
		15—39 years	40—59 years	60 years and over	total	15—39 years	40—59 years	60 years and over	total	15—39 years	40—59 years	60 years and over	total	
	MALES													
1	Infectious diseases	5.8	4.4	3.9	5.0	17.5	12.9	10.5	14.7	1.0	2.3	5.4	2.2	01
2	Neoplasms	0.4	1.8	4.4	1.6	9.1	36.3	130.2	40.3	1.9	14.2	85.3	21.1	02
3	Allergic and metabolic diseases etc.	7.5	15.6	28.3	14.0	8.3	15.3	28.9	14.4	0.2	0.5	2.3	0.7	03
4	Diseases of the blood	0.9	1.2	3.7	1.5	1.6	1.9	7.9	2.8	0.0	0.2	1.5	0.4	04
5	Nervous disorders and mental diseases	12.6	22.2	18.8	17.1	9.7	16.7	7.6	11.7	0.0	0.2	2.9	0.6	05
6	Organic nervous diseases (incl. cerebral hæmorrhage)	3.5	7.6	18.4	7.5	5.6	13.1	45.8	15.5	0.5	4.2	66.6	13.7	06
7	Heart diseases and hypertension	4.7	19.5	79.5	23.0	6.6	35.2	120.3	36.9	0.7	14.2	145.2	31.3	07
8	Diseases in arteries and veins	5.5	16.2	39.9	15.3	14.7	30.5	47.6	26.0	0.1	0.6	23.0	4.4	08
9	Colds and influenza	104.5	86.9	84.3	94.7	5.9	3.3	2.9	4.4	0.0	0.2	3.0	0.6	09
10	Other diseases of the respiratory system	38.7	52.0	75.5	49.8	14.2	23.8	47.0	23.5	0.2	1.3	16.1	3.4	10
11	Ulcer and other gastric and duodenal dis.	29.6	46.6	40.1	37.5	35.5	69.0	60.2	51.3	0.2	1.6	4.2	1.4	11
12	Other diseases of the digestive system	30.9	37.3	53.6	37.2	89.1	103.3	140.7	103.3	0.4	1.3	8.8	2.2	12
13	Diseases of urinary organs and male genitals	4.0	8.7	33.4	10.8	28.3	48.9	153.6	58.0	0.4	1.4	24.1	5.0	13
15	Skin diseases	24.7	21.7	22.4	23.2	15.7	12.5	11.1	13.8	0.0	0.0	0.2	0.0	15
16	Rheumatic diseases	20.9	71.7	130.9	58.2	9.0	19.1	31.5	16.6	0.0	0.0	0.1	0.0	16
17	Other diseases in bones, joints and muscles	21.4	24.4	36.1	25.0	20.9	21.8	14.9	20.1	0.0	0.0	0.0	0.0	17
18	Other and ill-defined diseases	37.4	51.8	98.0	53.1	18.1	23.6	38.6	23.7	0.3	1.7	5.0	1.6	18
19	Accidents and suicides	18.6	16.4	12.6	16.8	116.5	84.6	83.8	99.7	5.7	8.4	16.6	8.6	19
	Total	371.6	506.0	783.8	491.3	426.3	571.8	983.1	576.7	11.6	52.3	410.3	97.2	
	FEMALES													
1	Infectious diseases	7.1	5.9	6.0	6.5	18.2	11.5	11.5	14.6	0.9	1.2	3.8	1.6	01
2	Neoplasms	3.1	7.3	6.3	5.1	41.1	94.8	111.8	73.2	2.3	17.9	76.8	22.0	02
3	Allergic and metabolic diseases etc.	13.0	26.0	42.9	22.5	39.1	57.7	64.3	50.4	0.2	0.6	3.9	1.0	03
4	Diseases of the blood	7.1	5.0	10.2	6.9	3.3	5.1	8.7	4.9	0.0	0.2	2.1	0.5	04
5	Nervous disorders and mental diseases	34.8	57.4	47.9	44.8	29.7	30.6	13.9	26.9	0.0	0.1	3.3	0.7	05
6	Organic nervous diseases (incl. cerebral hæmorrhage)	6.3	12.7	22.6	11.3	7.6	15.4	49.1	18.3	0.6	4.6	73.0	15.9	06
7	Heart diseases and hypertension	6.3	32.6	129.2	36.3	9.9	34.0	145.1	44.4	0.4	6.8	132.0	28.0	07
8	Diseases in arteries and veins	16.1	37.6	68.6	32.5	19.6	27.1	31.5	24.5	0.1	0.5	25.8	5.2	08
9	Colds and influenza	97.7	83.5	85.1	90.7	7.1	3.6	3.9	5.3	0.0	0.2	3.5	0.7	09
10	Other diseases of the respiratory system	45.3	61.0	81.5	56.9	14.2	16.9	34.4	19.0	0.2	0.8	14.5	3.2	10
11	Ulcer and other gastric and duodenal dis.	15.1	23.8	32.4	21.0	17.0	33.5	22.8	23.8	0.0	0.3	1.8	0.5	11
12	Other diseases of the digestive system	45.9	69.3	80.7	59.8	108.2	122.0	139.4	119.0	0.3	1.7	11.7	3.0	12
13	Diseases of urinary organs	11.9	17.3	31.3	17.1	16.5	23.7	31.0	21.8	0.3	1.5	7.4	2.1	13
14	Women's complaints	125.1	102.4	19.4	99.3	441.0	151.0	22.6	260.6	0.6	0.3	0.3	0.4	14
15	Skin diseases	24.2	25.7	26.2	25.0	8.8	12.8	15.2	11.4	0.0	0.0	0.3	0.1	15
16	Rheumatic diseases	26.4	103.0	204.9	83.1	12.1	34.7	49.1	27.0	0.0	0.0	0.2	0.0	16
17	Other diseases in bones, joints and muscles	33.5	52.2	63.4	45.0	12.5	15.4	12.1	13.4	0.0	0.0	0.1	0.0	17
18	Other and ill-defined diseases	51.2	73.3	128.6	72.0	36.7	31.7	34.9	34.7	0.3	1.4	5.7	1.7	18
19	Accidents and suicides	7.6	10.0	15.2	9.7	44.9	56.1	107.6	60.9	1.7	3.3	15.6	4.9	19
	Total	577.7	806.0	1 102.4	745.5	887.5	777.6	908.9	854.1	7.9	41.4	381.8	91.5	

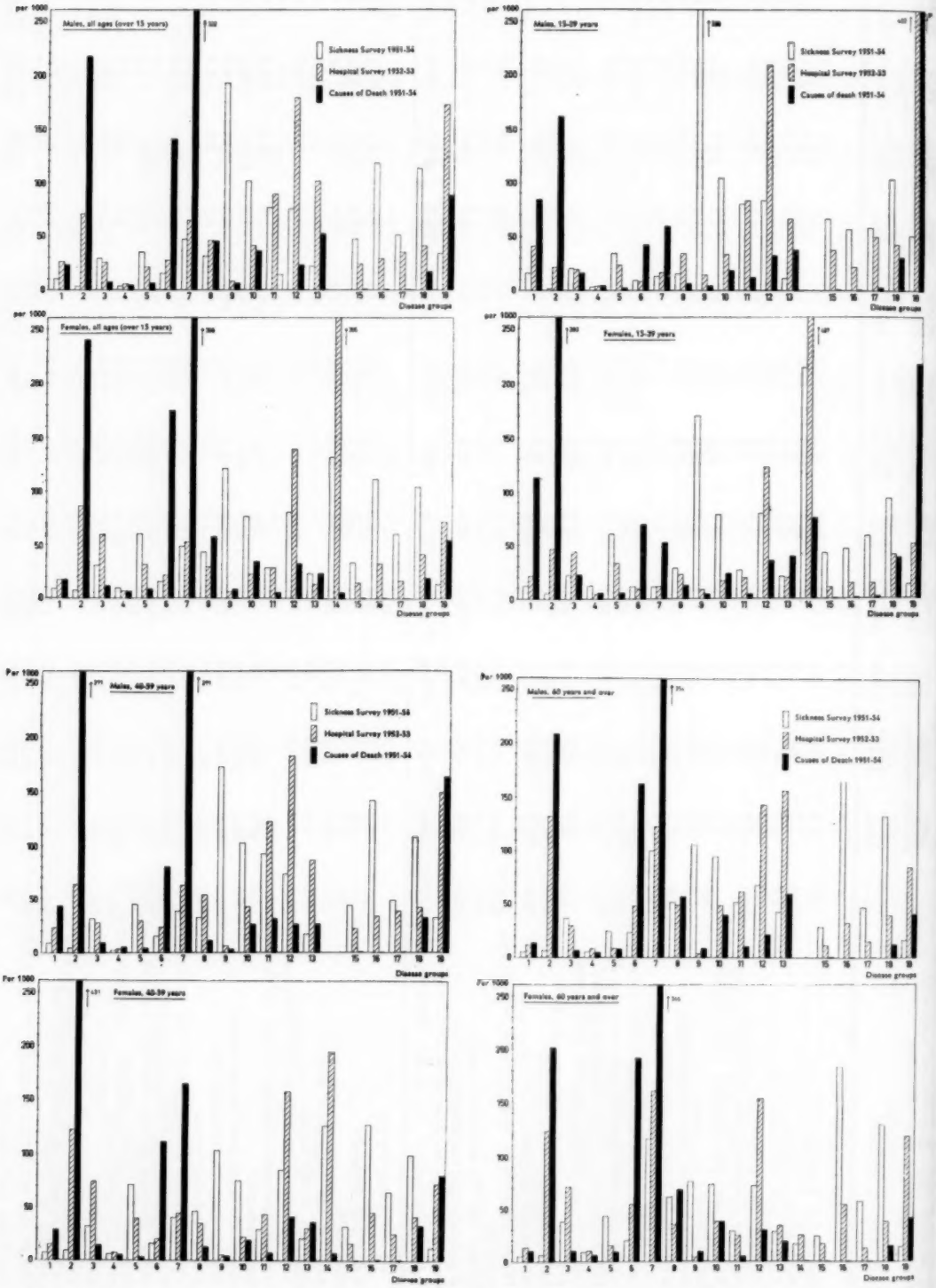


Figure 2. Distribution per 1,000 of Illnesses, Hospitalizations and Causes of Death. By Sex and Age.

Table III.
Estimated Population 1st July 1955 and 1. January 1960.

	Males		Females		Both sexes	
	1955	1960	1955	1960	1955	1960
	100					
15—39 years	7533	7771	7558	7749	15091	15520
40—59 years	5482	5647	5717	5846	11199	11493
60 years and over	2981	3270	3337	3746	6318	7016
Total 15 years and over	15996	16688	16612	17341	32608	34029
Under 15 years	6030	5958	5752	5668	11782	11626
Total population	22026	22646	22364	23009	44390	45655

a lower morbidity than weather with low temperature and higher humidity.

As to the *duration of the illnesses* a distinction is made between the number of sick days per person and per case of sickness. As regards the former, it has been found for occupationally employed that every male absentee averages 9.2 sick days per month and every female absentee 7.7 days. The period rises with age. On calculating how many days all employed, both sick and well, on an average are absent from work on account of sickness in one year, we get 7.40 days for males and 7.93 days for females. Females suffer from more ailments than males but they are of shorter duration. Of all sick persons an average of only one in six was so ill that work had to be neglected.

A separate census concerning the occurrence and spread of *the common cold* was made over a six-month period and comprized 15,858 persons. They were asked how they were usually affected by a cold — in this case not confining the inquiry to a single month.

Relatively more females than males catch cold, whereas those males who are liable to colds are more often attacked. The cold frequency decreases with the years, being highest in the young age group. Of all respondents 76.7 per cent state they are never absent from work on account of colds; of those who are, over 60 per cent are absent less than three days. The average absence is 3.07 days per annum.

The questionnaire contained a question, according to which the respondent was to state, whether he (she) considered his dwelling to be unhealthy (dark, moist, cold and/or overcrowded). The result was that 11.2 per cent of the dwellings were considered to be unhealthy, highest for the metropolitan area, 12.3 per cent. As might be psychologically expected, it was generally the females, who considered their dwelling to be unhealthy.

As might also be expected, the sickness frequency was higher in the bad dwellings. But the distribution of sickness according to sex and age in the bad dwellings was the same as in the material as a whole. And it was not possible to ascertain, that any diagnosis, or group of diagnoses, was prevalent in the bad dwellings.

During the three years of the survey some statistical inquiries were made that were actually outside the scope of the Morbidity Survey, such as: the taking of sleeping drugs, use of spetacles, diphtheria vaccination, dental treatment, relation of height to weight and consumption of tobacco. A special investigation of the living conditions of old-age people — 60 years and over — was also undertaken. Use was made of an opportunity, when there was direct access to get into conversation with a large section of the population, to procure information that was wanted and that might be of general interest.

About 8 per cent of the adult population use *sleeping drugs*, 5.1 per cent of the males and 10.2 per cent of the females. The consumption increases considerably with age, and over the age of 65 years every fourth female and every eighth male takes soporifics more or less frequently.

Spectacles are worn by 46.5 per cent of all adult males, 13.2 per cent of them constantly. For females the figures are somewhat higher, 51.8 and 17.4 per cent respectively.

Females consult their *dentist* more frequently than males. Of those visiting the dentist only 6 per cent of the males and 7 per cent of the females had teeth requiring no treatment.

In order to ascertain whether there was any connection between the body weight and sickness of the respondents the *heights and weights* indicated by judgment of the interviewers were statistically treated. The respondents were registered as tall, medium, small, and in the weight groups: stout, medium, thin. There seems to be some connection between "stout", that is to say overweight, persons and certain diseases (metabolic disorders, sciatica, heart disease etc.). The material also showed that there are more overweight women than men, and that the Capital has most tall men and the rural areas the most stout women. The height of the respondents decreases as one moves from the young to the old age groups, whereas the weight does not become

less until the age of 60—70 years. In this connection it should be borne in mind that the stature of the population is increasing: the former generations were smaller than the present ones.

The following are the main results of the very comprehensive investigation of the country's *tobacco consumption.*

78 per cent of all adult males are smokers, 8 per cent have smoked earlier and 14 per cent have never smoked. The figures for females are 40, 14 and 46 per cent respectively. Of the 78 per cent male smokers 23 per cent smoke cigarettes, 38 smoke pipes, 9 cheroots and 7 per cent cigars.

A separate inquiry was made as part of the Sickness Survey, concerning 2,716 *persons of 60 years of age and above,* corresponding to ½ per cent of the total Danish population of that age-group.

The morbidity was caused chiefly by the chronic, age-conditioned forms of sickness: diabetes, apoplexy, heart-disease, hypertension, vascular diseases, rheumatism, and affections of eyes, and ears. For people over 70 years heart- and kidney diseases nearly double.

193, or 6.1 per cent males, and 8.1 per cent females had not full validity. Applied to the total Danish population above the age of 60, this means, that 44,000 have not their full validity.

Of all old people in the inquiry, 11 per cent are under special care or receive a certain attention; and as to their housing, 46 per cent in the towns live on the ground floor, but 11 per cent on the third floor or higher.

As to the old people's occupations, it was found that 55.9 per cent of the males and 16.3 per cent of the females had occupational work. Among the old people the per cent of employment is highest in the rural areas.

Of their spare-time occupations 20 per cent of the old people declared they do work of a manual kind, *i.e.,* of rather an active nature.

By means of the population figures in Table III and the rates in Table I, total figures of each single diagnosis occurring in Denmark in the specific age- and sex-groups can be calculated.